Clinical Selections in

DERMATOLOGY

AND

MYCOLOGY

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By

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With Contributions by
Thirty-six Specialists
from Various Lands



CHARLES C THOMAS PUBLISHER
Springfield Illinois U.S.A.

CHARLES C THOMAS PUBLISHER

Bannerstone House

301–327 East Lawrence Avenue, Springfield, Illinois, U.S.A.

Published simultaneously in the British Commonwealth of Nations by

BLACKWELL SCIENTIFIC PUBLICATIONS, LTD., OXFORD, ENGLAND

Published simultaneously in Canada by

THE RYERSON PRESS TORONTO

Library of Congress Catalog Card Number: 55-11249

Printed in the United States of America

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DEDICATED TO THE MEMORY OF

WILLIAM F PETERSEN

The lights went out in the big lecture hall. Up forward on the white screen flashed a curious design of black lines twisting and etching their way through the white background. We in the audience were bewildered. What was the meaning of those numbers spread out along the ordinates and abscissas of the huge chart? Suddenly the point of the marker indicated the very lines about which we were puzzled. At the same time a soft voice almost inaudible reached our ears. As the voice grew stronger it breathed life into the lines and figures on the chart before us. We realized then that we were listening to words of cosmic meaning, for they were giving substance to the ideas and observations of Hippocrates as well as to thoughts that soared to the sun and stars. No line on the chart was punctuated by a point in time. It was the microcosm scintillating in the endless space of the macrocosm. William Petersen had caught a glimpse of things that are and things to come.

Preface

THIS WORK is almost entirely a creation of physicians and scientists of the various countries which comprise the Americas. Controversial opinions and original ideas are purposely emphasized in order to promote discussions leading to a better understanding of dermatologic problems.

The climate and mode of living prevalent in the vast area extending from Mexico to the northern border of Argentina have combined to involve the skin in affections predominantly caused by plant and animal parasites, with the result that the relative incidence of "classic" or cosmopolitan" dermatology in this region is lower than in the lands of the temperate zone. The practice of dermatology and mycology in subtropical and tropical America is by no means limited to the skin and its appendages, for due to the prevalence of abscesses and ulcerations, it really goes right down to the bone.

The incidence of pyogenic infections and parasitic diseases such as impetigo and scabies has decreased in some parts of these lands due to the more general adoption of hygienic measures and the use of the newer antibiotic drugs, the unavailability and prohibitive cost of which in other parts of the Americas have maintained these disorders at a high level.

We seem to have passed through the age of clinical analysis in which diseases were studied and described and are entering upon a period of synthesis in which clinically and morphologically similar disorders are being reduced to synonymy and etiologic clarity is being established.

Other channels for our creative energy are leading to new horizons. We are arriving at a better understanding of the part played by enzymes, vitamins, proteins, and minerals in the cutaneous economy Newer methods of staining and fixation in conjunction with the use of ultrasonic vibrations and the capillary and electron microscope are daily revealing a clearer picture of

the living skin. We are beginning to think in terms of physiology and biochemistry Formerly we saw only "das Gewordene" of Goethe now we are catching glimpses of "das Werden."

One of the first to sense the constant flux and alternating rhythm of the biologic processes of the body was Hippocrates Millenia later Kyrle recognized the vital character of many of these reactions in the skin and correctly interpreted their biologic significance. The mechanisms whereby Hippocrates attempted to account for man's reaction to his environment and those that Kyrle conceived to explain the histologic changes he observed under the microscope have been vitalized and infused with new ideas by Petersen. His conception of vasospasm is slowly assuming its proper place as one of the principal precipitating factors in the constellational environment responsible for the production of disease.

In the first chapter of this book, Petersen's concept of vasospasm and its principal causes are elaborated by Duggan, himself a pioneer in this field, especially in the practical application of Petersen's principles to the treatment of disorders of the eye. I have then attempted to give a summary of my experiences with vasodilators in the treatment of diseases of the skin and to point out the influence, if any of arteriolar spasm on the various disorders discussed by some of the contributors.

Pertinent references to the literature have been placed at the end of each chapter and a list of the books which I have particularly consulted will be found at the end of the book. The word "disease" as used in the text implies, unless otherwise indicated, a disease of the skin or a systemic disease accompanied by cutaneous manifestations.

English and Spanish equivalents for words and phrases that easily evoke confusion are given with the English equivalent placed first. The occasional use of popular terms in English, Spanish, and Portuguese to designate names and symptoms of diseases has as its purpose the promotion of mutual understanding among our colleagues.

I assume full responsibility for the translation into English of the contributions written in Spanish and German.

The treatment of each disease is limited to the use of as simple remedies as possible, to the exclusion in many instances of equally efficient ones, the cost and unavailability of which prevent their employment in many of the remoter areas of the Americas. The drugs used are listed chiefly in the *United States Pharmacopeia* and the *National Formulary* the designations for which are given as U.S.P and N.F., respectively Wherever a drug is indispensable, whether for use as a topical application or for oral or parenteral administration, it is entered in the text as such.

San Jose Costa Rica FREDERICK R. SCHMIDT

Acknowledgments

MY FIRST acknowledgment is to the men and women of many countries who have so generously expended their time and energy in contributing to this volume. They continued their cheerful cooperation and helpful suggestions throughout the preparation of the manuscript in spite of the difficulties of communication and of exchange of opinions peculiar to the production of a book of this character

The friendship and acquaintance with these physicians and scientists of many lands is the real incentive for publishing this book, for it is my sincere hope in this manner to repay at least to some degree, a debt to these friends and colleagues for having so abundantly lavished their time and hospitality on me during my journeys throughout the Americas.

Dr Roberto Jaramillo Bruce of Santiago Chile, was one of the first men I got to know in South America. His personality and scientific acumen brought me to admire and respect highly the achievements of the individual physicians of the Americas who have reached eminence in the profession through their own efforts and in the face of such obstacles as inadequate laboratory and library facilities.

I wish to thank the following physicians for their courtesy in extending the facilities of their hospitals and clinics to me Guillermo Basombrio, Julio Borda, Luis Pierini, and Marcial Quiroga, of Buenos Aires, Argentina, Victor Villarejos, of La Paz, Bolivia, Luis Prunes, of Santiago, Chile, V Pardo-Castello of Havana, Cuba, Jose Barberubio and Fernando Latapi, of the Republic of Mexico and Pedro Weiss, of Lima, Peru.

I am greatly indebted to Dr Pena-Chavarria for allowing me access to the wards and facilities of the San Juan de Dios Hospital in San Jose, Costa Rica, of which he is Director and to Dr Zamora-Segura for granting me the use of the splendid hospital library Dr Julio Ovares, head of the department of dermatology

in the hospital, has earned my lasting gratitude and appreciation for instruction in the diagnosis and treatment of tropical skin diseases as well as my admiration of his skillful and kindly care of patients. Dr Alejandro Gonzalez Lujan has been most kind in making available the excellent library of the Hospital Seguro Social, and Dr Elias Bonilla Dib has kindly granted me the privilege of attending his various clinics.

I am very grateful to my wife, Virginia, for her aid in preparing and typing the manuscript, and I wish to thank Helen Westermann for her careful retyping.

I am also very grateful to Mr Charles C Thomas and Mr Payne Thomas for their many courtesies and helpful suggestions.

F R. S

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Vasospasm as an Etiologic Factor in Disease

By

Walter F Duggan

> *So in one place the blood stops, in another it passes sluggishly in another more quickly The progress of the blood proving irregular all kinds of irregularities occur*
>
> HIPPOCRATES

FOR MANY years disease was so closely associated with positive etiologic agents such as bacteria, viruses, parasites, toxins, and poisons that it was difficult to believe in a cause prefixed by a minus sign. However such a concept led to the discovery and treatment of the avitaminoses. The reactions occurring within the body were almost completely forgotten. It was not until Cannon formulated his concept of homeostasis that we really began to understand that reactions occurring within the body could also be a cause of clinical disease.

Among the homeostatic systems is the vascular system. Throughout life, various exogenous and endogenous factors regulate the tone of the arterioles so that normal capillary and tissue function is the result. I pointed out that when homeostatic reactions become stabilized outside of the zone of normality pathologic physiology occurs followed shortly by pathologic anatomy Changes in function and structure become manifest, and clinical disease may be said to be present.

THE NATURE OF VASOSPASM

By vasospasm I wish to indicate spasm of only the smallest arteries and the arterioles. Due to this arteriolar spasm, the capillaries which normally receive blood from the spastic arteriole

become dilated and abnormally permeable so that transudation of plasma, white cells, and erythrocytes may occur

Only spasm of arterioles and smaller arteries will be considered here. Such diseases as arteriosclerosis, thromboangiitis obliterans, and Raynaud's disease will not be discussed. In individuals who have a pre-existing chronic vascular disease, spasm can be superadded, as in temporal arteritis Several possibilities exist, depending on the degree and duration of the vasospasm.

1. If the arteriolar spasm is intense but of short duration, there may be total loss of function followed by complete return to normal function without any permanent pathologic changes.

2. If the spasm is intense and prolonged, an infarct results with complete and permanent loss of function and atrophy of tissue normally supplied by the spastic arteriole.

3. If the spasm is moderate and of short duration, there are transitory attacks of impairment of function with normal function between attacks and slight pathologic changes.

4. If the spasm is moderate but prolonged, repeated attacks (or one very prolonged period of spasm) lead to some permanent impairment of function, with definite permanent pathologic changes in the involved tissues. These permanent pathologic changes may be atrophic or hypertrophic depending upon the degree and duration of localized tissue anoxia. In fact, a lesion may show atrophy in the center and hypertrophy at its edges. In the choroid of the eye both depigmentation and pigmentation can occur as a result of the stimulus of anoxia or hypoxia in acute exudative choroiditis.

Mild degrees of vasospasm are probably occurring constantly as part of the homeostatic mechanism concerned with regulating both blood pressure and supply of oxygen-containing blood to the various tissues and organs of the body However as Nedzel and others have pointed out, the differences between these transient, minor and normal physiologic fluctuations in the tonicity of the arterioles and the pathologic degrees of true vasospasm are of degree rather than of kind.

Due to arteriolar spasm, the capillaries dilate, and their permeability is increased so that transudation of plasma or plasma and

blood cells takes place in the capillary walls. According to Ricker three types of transudation occur

1. Prestasis, in which only plasma passes through the capillary walls: urticarial lesions develop as in transient lesions due to allergy

2. Peristasis in which plasma and white blood cells particularly lymphocytes, pass into the perivascular tissues. Peristasis occurs in acute iritis, choroiditis, retrobulbar neuritis, episcleritis, erythema nodosum, lesions attributed to viruses, and in cerebral and ocular complications which can follow the use of various vaccines.

3. Stasis, in which erythrocytes pass through the capillary walls. Stasis results in purpuric lesions and is the cause of some types of retinal hemorrhages as well as of disciform degeneration of the macula.

It will be shown later that these capillary changes can occur without arteriolar spasm but when arteriolar spasm does occur the capillary changes of increased dilatation and increased permeability are secondary to arteriolar spasm.

Whatever the etiologic factor may be in vasospasm, the ultimate result is the same there is a decrease in the supply of oxygen to the tissues, and tissue anoxia or hypoxia occurs. Anoxemia need not be present. However if anemic anoxemia is also present as occurs in severe hemorrhage or if relative alkalosis is present, tissue anoxia or hypoxia will be intensified.

The larger arteries act chiefly as mechanical tubes and rarely undergo spasm. Vasospasm of clinical significance probably does not occur in arteries larger than the coronary arteries or the branches of the anterior middle, and posterior cerebral arteries. Spasm has often been seen in branches of the central retinal artery However it must not be forgotten that the larger arteries receive their oxygen and nutrition through the *vasa vasorum*. We do not know whether these tiny vessels can undergo spasm, but they can become thrombosed. Closure of the vasa vasorum may be a factor in the development of periarteritis nodosa.

It is quite likely that spastic closure of vessels of the size of the central retinal artery or its branches gives rise to many diverse and superficially different lesions. Many rare and com

mon diseases of the central nervous system, including infantile paralysis and multiple sclerosis probably have a vasospastic pathogenesis Many symptoms and diseases associated with a sudden change in the weather are also of vasospastic origin.

Clinically it is often difficult to distinguish between thrombotic closure and spastic closure of a small artery or arteriole. However in my opinion, vasospasm probably has occurred

1. When transient sensory motor or other symptoms occur

2. When rapid amelioration of signs and symptoms occur soon after the use of vasodilating drugs

3. When spasm can be seen as in the case of spastic closure of the central retinal artery or its branches and when it disappears *soon after the use of vasodilators.*

4 When in a series of cases such as in acute retrobulbar neuritis or in Bell's palsy for example improvement is more rapid or a complete return to normal function is effected more rapidly than in a comparable series of cases which received no treatment or were subjected to some other type of therapy

It has commonly been assumed that acute spastic closure of a small artery or arteriole results in narrowed arteries or arterioles with ischemic tissues This is not so. In spastic closure of the central retinal artery there is a marked edema of the retina, the veins are engorged, small hemorrhages may be seen at times, and the spastic vessel is threadlike, or it may be constricted at only one spot. The capillaries cannot be seen, but the increased permeability of their walls explains the origin of the edema and hemorrhages. In other words, various stages of prestasis, peristasis, and stasis are present.

Moreover if a single one of the four main branches of the central retinal artery undergoes spasm, edema of the retina will be limited to the region of the retina supplied by that branch, and the defect in the visual field will correspond to the part of the field which corresponds functionally to that part of the retina which is involved.

It has been intimated by many writers that spasms of very small arteries are not clinically significant. This is not true The central retinal artery is not larger than a hair in diameter yet if this artery undergoes spasm almost total blindness occurs in that

eye. If the superior or inferior division undergoes spasm, either the lower or the upper half of the field of vision is lost. If the temporal or nasal division of the superior or inferior retinal artery becomes spastic, a quadrant of the field of vision is lost. For years, Alvarez has stressed the point that closure of smaller cerebral vessels leads to tiny "shocks."

Also, the fact that normal retinal arteries do not dilate appreciably or measurably following the use of vasodilators has been offered as evidence that vasodilators do not dilate arteries or arterioles. However all arteries and some arterioles have an outer layer the adventitia, and some have a connective tissue sheath. This anatomic characteristic will of necessity limit the degree to which they can dilate, but under the influence of vasoconstrictor drugs or stimuli their lumina can be almost completely obliterated. Therefore, vasodilator drugs can only show their full effect on spastic vessels.

Moreover vasospasm must be marked to cause detectable functional changes. In many patients who have hypertension, it is possible to see localized narrowings of the retinal arteries without any disturbance of function and without any accompanying edema or retinal hemorrhages. In these cases, sufficient blood must reach the capillaries to maintain normal function. The degree of spasm necessary to produce changes in function and structure will be discussed later in the section dealing with experimental work on vascular spasm.

It has been stated that arteriolar spasm can not cause the capillary changes mentioned above. However Moon pointed out that,

Suitably large doses of adrenaline will produce a condition of circulatory failure undistinguishable from shock Adrenaline may produce maximal arterial constriction of such degree that the tissues suffer from anoxia. If the lack of oxygen is of sufficient duration and degree, atony of the capillaries and vessels will develop in the area affected. This will lead to concentration of the blood and decreased blood volume by transudation of plasma and to stasis of blood in areas where maximal dilatation of the minute vessels has occurred."

Gormsen reported the case of a 42 year old asthmatic who gave himself 60 mg. of adrenaline subcutaneously Death occurred in

To understand histamine is to understand allergy Albus, on the basis of physiologic and pharmacologic studies, has suggested that the term "histamine-susceptible constitution" be substituted for the term "allergic constitution."

THE VASCULAR BASIS OF ALLERGY

In 1946 I discussed and described the vascular basis of allergic ocular lesions. In many cases, physical agents, especially exposure to cold, were of etiologic significance. At that time I stated "To me, allergy includes all of those aseptic or abacterial lesions in which the basic pathologic processes can be reduced to the common denominator of either increased capillary permeability or excessive contraction of smooth muscle or both. Smooth muscle, of course, includes the smooth muscle in the arterioles The concept of allergy and its treatment which I propose to develop must include as etiologic factors all influences—chemical, nervous, humoral, or climatic—which can cause either increased *capillary permeability or smooth muscle spasm or both. Since* most of the smooth muscle in the eye is found in the walls of the arteries and arterioles, I think that allergy of the eye can be interpreted as a problem in vascular physiology

It is obvious that treatment should be primarily directed toward removing the arterial spasm Instances of such diverse lesions as herpes zoster ophthalmicus and herpes cornea, paralysis of various ocular muscles, spasm of the central retinal artery or its branches, optic and retrobulbar neuritis, acute iritis and iridocyclitis, acute exudative choroiditis, choroidosis centralis serosa, episcleritis, and other lesions were reported in which only vasodilator drugs were used. Earlier I had reported a rapid cure of four cases of Bell's palsy of the facial nerve and several cases of tobacco amblyopia with vasodilator therapy

While for a long time other investigators and I had been treat ing many ocular lesions which were actually manifestations of allergy or hypersensitivity with vasodilators on the assumption that arteriolar spasm with secondary capillary changes was the primarily important pathologic lesion it was Ratner who first used the term "arteriolar spasm to designate the basic pathophysiologic lesion in allergic and hypersensitive reactions.

Ratner believed that wheals, the Arthus phenomenon, and the response to histamine were all due to arteriolar spasm and that the antigen-antibody reaction also caused arteriolar spasm. Petersen, likewise, was one of the first to state that lesions directly associated with sudden changes in the meteorologic environment were due to arteriolar spasm with resulting tissue changes and associated tissue anoxia.

It is a well-known fact that the symptoms and lesions of anaphylactic shock are constant for a given animal species whatever the sensitizing antigen may be and that they differ sharply in the various species. Also in animals killed with histamine, the symptoms and lesions are nearly always identical with those of anaphylactic shock in the same species

Topley summarized the situation in these words "Histamine is a relatively simple substance of known chemical constitution. It can hardly be a mere coincidence that on intravenous injection it mimics so closely the syndrome produced by the infection of a nontoxic antigen into a sensitized animal."

After noting that the tissues which are involved in anaphylactic shock are the same as those that are sensitive to histamine, he continues as follows whether the cells that are injured and liberate histamine are themselves histamine-sensitive, whether minimal injury may so disturb the internal economy of cells that they become reactive to their own histamine, or whether we should locate the injury and liberation of histamine in one type of cell, (and) the response to the liberated histamine in another are problems which are not soluble at the moment.

The experimental work of Horton, Brown, and Roth would support Topley's third possible mode of action, because when their subjects hands were immersed in cold water histaminelike systemic reactions such as flushing of the face, fall in the systolic and diastolic blood pressure rise in pulse rate, increase in the free and total hydrochloric acid, and a tendency to the development of syncope did not occur if a tourniquet was kept on the arm and did occur after the tourniquet was removed or if a tourniquet was not used. Moreover subcutaneous injection of 0.5 mg. of histamine not only produced the same systemic reactions, but the patients were unable to distinguish between the systemic mani

festations produced by immersion of the hand in cold water and those produced by subcutaneous injection of histamine."

Urbach, Hermann, and Gottlieb believed that hypersensitiveness to cold may be due to histamine and stated under given pathologic conditions, the tissue's own protein can undergo alteration, and under the influence of physical agents this altered protein produces a histaminelike substance which may cause intense cutaneous manifestations."

Schmidt treated such diverse dermatoses as pruritis of the legs with peripheral vascular disease, summer prurigo erythema multiforme, toxic erythema from drugs, pityriasis rosea, purpura, and other lesions and obtained satisfactory improvement in many of his cases with vasodilators

Harkavy in a paper on vascular allergy concluded that not only the bronchi but the myocardium, serous membranes, joints skin, and nervous and hemopoietic systems may be involved in the more generalized vascular reactions and that distinct syndromes may arise which may be reversible or irreversible. He regarded these conditions as hyperergic vascular responses.

Regarding allergy and histamine, I summarized the relationship as follows

"All the available evidence indicates that allergy resembles a localized manifestation of histamine poisoning Tiny amounts of histamine may be of physiologic importance in regulating capillary permeability In large amounts, histamine acts as a toxin by increasing capillary permeability beyond physiologic limits. It causes tissue anoxia. Lack of oxygen can cause the same type of lesions. Oxygen is a physiologic antagonist of histamine. All agents which can cause increased capillary permeability and tissue anoxia may be concerned in the production of allergic lesions." As Moon stated many phenomena called toxic are essentially anoxic. Allergy must be included among these phenomena Any factors which would tend to relieve capillary and tissue anoxia should be of value in the treatment of allergy" Among these factors vasodilators are of primary importance.

WEATHER AND VASOSPASM

Petersen was the first to make an extended study of the effect of sudden changes in the weather in initiating clinical disease. Much earlier Hippocrates had noticed that such a relationship existed. This relationship was also noticed in cases of eclampsia by Fuerstner and Sargent.

According to Petersen, a polar infall or passage of a cold front (rising barometric pressure and falling temperature) causes in the body the ARS phase (A = anabolism, R = reduction, S = spasm of arterioles or of any smooth muscle) When the ARS phase occurs, there is anoxia or hypoxia of an organ, tissue, or portion of a tissue due to arteriolar spasm as well as edema due to increased capillary permeability Smooth muscle spasm and increased capillary permeability also occur in the "allergic lesion, so that lesions due to changes in the weather may represent an allergic or anaphylactic reaction to the weather as was called to my attention by Sargent.

Opposite changes occur with the passage of a warm front or tropical front, and Petersen has designated these changes as the COD phase (C = catabolism, O = oxidation, D = dilatation of arterioles or relaxation of smooth muscles in other systems than the vascular system)

The ARS phase is stimulating up to a point unless the spasm is too intense or too prolonged, in which case various lesions may occur in *any* organ or tissue of the body This is of special importance as a pathogenic factor in nervous and emotional episodes.

Other changes which accompany the ARS phase are Elevation in blood pressure and blood sugar level, increased activity of the adrenal gland, decreased tension of carbonic acid in the blood, and relative alkalosis with dehydration of the tissues. The capillaries are less permeable unless the arteriolar spasm is too intense or prolonged, in which case they become more permeable. If homeostatic mechanisms cannot control these various changes, any one of many diseases may develop. In other words there is a shift from the zone of pathologic physiology to the zone of pathologic anatomy and this change is sometimes irreversible.

At times, death of a tissue, an organ, or the whole body may occur

Changes which accompany the COD phase are lowering of the blood pressure and of the blood sugar level, increased activity of the thyroid, increase in the tension of carbonic acid in the blood, and relative acidosis with hydration of the tissues. If these changes go beyond physiologic limits, clinical disease and vascular thromboses occur

A warm front usually occurs slowly and gradually so that it is more difficult to correlate it than a cold front with the onset of a disease The cold front is usually sudden in onset, and almost the exact time of onset can be determined.

It must also be remembered that oxyhemoglobin gives up its oxygen more readily in the presence of heat and acidosis, and it dissociates less readily in the presence of cold and alkalosis so that oxygen is less available to the tissues with the passage of a cold front (ARS phase) and more available to the tissues with the passage of a warm front (COD phase)

Furthermore, in the passage of a cold front with a rising humidity or actual rain, the impact of the cold wet air upon the skin will cause the production of histamine in the skin, so that this substance in turn will tend to increase the arteriolar spasm and increase beyond normal limits the capillary permeability In other words being exposed to cold wet air differs only quantitatively from falling into cold water

Taylor and Dyrenforth, and Taylor have studied the effect of cold water on humans and of cold on animals. The conclusions in both papers are essentially the same, namely that " chilling of the body surfaces without compensation leads to certain morbid changes within the body They are caused by peripheral vasoconstriction with attendant peripheral stasis and anoxemia, by lowered leukocyte response and by impairment of the phagocytic capabilities of the fixed tissue cells, including that of the nasal mucous membrane." This explains the genesis of the common cold or upper respiratory infection. The organism is a secondary invader- the primary vascular changes in the nasal mucosa are the real cause of the cold.

This interpretation of the common cold was hinted at by Fox and Livingston several years ago and stated very definitely by an

unknown author in an ironic editorial entitled "Pass the Kleenex." This author said. "Contrary to the general opinion that most colds are acquired by direct contact, colds are the result of exposure of the body to drafts, low temperatures, and moisture with resultant vasoconstriction of the nasopharnynx."

The literature on this subject is voluminous. One can best sum it up in Petersen's words from his paper on ocular physiopathology and weather His comment was " any extreme in the environmental situation, whether toward cold or toward heat, is apt to find reflection in clinical symptoms for the simple reason that such changes entail major vasomotor adjustment. While any one of many environmental factors may act as a precipitating force, the weather episode, on the background of season, is the most common of the energy impacts that are effective, for the biologic effect is likely to be prolonged. The vascular spasm may exist for hours or even days, is subject to summation with repetition of environmental change and is, in addition, universal in its effectiveness in the population at large The meteorologic episode is universally effective, and the clinical reflection will be found in any organ or tissue."

Mills stated. "Short cycle weather changes bring startling alterations in health and physiologic functions alterations with which physicians should be thoroughly aware" and, a few years later I said "I believe that man's reactions to the ever changing sea of air in which he lives constitute, in an unstable person, one of the major causes of disease and that allergy or better vasoneuropathy of physical origin (Urbach) is a pathologic reaction to a sudden change in this sea of air"

No one will dispute the fact that acrocyanosis in children is due to undue hypersensitivity of the afferent digital vessels to cold, with spasm of the arteries and arterioles, increased capillary permeability and subepithelial venous stasis. Whether this is a direct response to cold or indirect through the mediation of histamine was not stated by Learmouth, but he suggests using vasodilators and advises against sympathectomy since the condition improves after puberty

If cold weather can directly cause vasospasm of the digital arteries and arterioles in acrocyanosis and if it is due to a histamine

agent formed in the skin, there is no reason why a similar mechanism should not be the cause of vasospasm elsewhere in the body when the histamine-sensitive cells are located in arterioles and capillaries elsewhere in the body

EXPERIMENTAL WORK ON VASCULAR SPASM

The best presentation of vasospasm from the viewpoint of the experimental pathologist has been given by Nedzel.

According to Nedzel, normal function (homeostasis) depends on proper functioning of the autonomic nervous system the endocrine glands, and the chemical and metabolic processes of the body The changing behavior of these three systems is reflected by the vascular system, particularly the arterioles and capillaries, since the capillaries are the final medium through which oxygen and foodstuffs reach the cells and waste products are carried away *He believed that it is reasonable to concentrate* on the terminal vascular segments as the final regulators of the functions of the cells in adjusting to the changing demands of their activities. The function of the vascular bed is to sustain and maintain normal life and function. Any inadequacies in the behavior of the terminal blood vessels will lead to impaired function, with resulting injury of particular groups of cells and the consequent production of disease.

Based on the results of frequent injections of small amounts of pituitrin into animals and a study of the lesion produced, Nedzel stated

"The transient variations in the resistance of the small blood vessels depend on the changes in tone of their walls. Hypertone and hypotone each (of) which may occur simultaneously in the whole body or in a large part of the body interferes little with the passage of blood to the tissue, and hence does not impair the process of nutrition.

"Another type of reaction is vascular spasm. It is an exaggerated state of hypertone, and it is limited to a certain region, organ or part of the body or even to one artery Spasm, in this sense, is always a localized phenomenon, a pathologic occurrence a diversion from the average amplitude and size of the normal ARS phase of Petersen the local phenomenon of vascular

spasm means practically a complete stop or a greatly diminished blood supply to the particular region during a definite time interval, shorter or longer but always exceeding the normal demand imposed by the environment.

" Vascular spasm is purely a functional phenomenon which is manifested by different pathologic symptoms. Yet (spasm) if greatly pronounced, or prolonged, or both, may precipitate disease in the organ or region in which the disturbance is centered. This view has both clinical and experimental evidence to support it

"As the metabolism of the cell is dependent on oxygen, any appreciable diminution in available oxygen precludes normal cell function. For this reason, anoxic phenomena become increasingly important in studies of pathologic conditions of the human body as well as in therapy

"The functional activity of the vascular bed appears to be of much significance in the development of many diseases, the etiology of which is attributed to other causes. Many different diseases themselves and different symptom-complexes can be explained on a vascular basis.

Basic disturbances—spasms in vascular beds—appeared (in animal experiments) in different regions and organs in varying degrees, thus leading to the formation of lesions in widely separated organs. These lesions are bases for different diseases, and yet their etiology is the same any factor which leads to vascular episodes in the body may cause one or another of several diseases, diseases which are very different clinically in their localization and manifestations.

Nedzel also stated that some workers had evoked allergy as the cause of multiple sclerosis and acute rheumatic fever and that his work and that of others showed that the pathologic lesions in these disorders could be due to transitory periods of localized anoxia.

Throughout his presentation, he states repeatedly that sudden changes in the meteorologic environment constitute a common cause of anoxia due to vascular spasm, particularly in patients with an unduly labile vascular system. Such patients would be allergic to their environment. Finally he mentions that disease is due to an inherited pattern of vascular instability

OTHER EVIDENCES OF VASOSPASM

The concept of arteriolar spasm as a cause of lesions in various organs of the body is not new Many such instances can be found in the literature although only a few will be mentioned here.

Among the unusual conditions in this category are acute retrobulbar neuritis, multiple sclerosis, shock and death following the subcutaneous injection of as little as 60 mg. of adrenaline, ocular manifestations associated with serum sickness and insulin shock therapy some cases of Pick's disease and circumscribed areas of myelin in the white matter of the brain.

Walker recently reported that "whereas 90 per cent of all migraine and Ménière conditions are allergic, only about 50 per cent of those diagnosed clinically as epilepsy or as disseminated sclerosis are true allergy" Walker based these conclusions on the experimental finding that the patients whom she classed as allergic reproduced symptoms or signs of their particular disease when given histamine-acid phosphate by electrophoresis

There are scores of reports of patients who had a spastic closure of the central retinal artery or one of its branches in whom the early use of vasodilators brought about a rapid dilatation of the spastic vessel with restoration of a normal fundus picture and the return of normal vision.

The amblyopia which follows hemorrhage has been recognized as a clinical entity since the time of Hippocrates. Generalized vasospasm which occurs as part of the homoostatic mechanism concerned with maintaining an effective blood pressure and which is exaggerated to a pathologic degree in the retinal arteries or the arteries in the optic nerves is the cause of the amblyopia. It is not due to an unknown toxin." If there is a "toxin," the culprit is epinephrine

The first phase of acute pancreatitis is regarded as an edema of ischemic rather than inflammatory origin. The improved results with current therapy in this disorder would seem to support this theory of pathogenesis.

Also, the subretinal macular lesion which I named choroidosis centralis serosa is considered of angiospastic origin by many ophthalmologists. Most of these writers, including myself have obtained rapid amelioration of symptoms following the use of vasodilators.

Excess or deficiency of the many endocrine secretions may alter the reactions of blood vessels, particularly during pregnancy or menstruation. Vascular spasm occurs during both conditions and can be of serious consequences in eclampsia and other toxemias of pregnancy The effective use of vasodilators in patients with eclampsia has been reported.

While improvement following the use of vasodilators in lesions due to vasospasm has been explained by many clinicians as *post hoc ergo propter hoc* reasoning, it can also be stated that every case of pneumonia which improves following the use of antibiotic drugs is also explainable by *post hoc ergo propter hoc* reasoning. In the final analysis we deal with individual cases. I agree with Tortella who in discussing vascular spasm and intravascular thrombosis, stated that the lesions which respond to vasodilators are due to vasospasm and that the response to this type of therapy supplies the data necessary for a differential diagnosis.

Many lesions due to vasospasm have been and are still considered due to focal infection. The so-called theory of focal infection should be discarded. I am fully in accord with Reimann and Havens who stated " in the light of present knowledge, the removal of such local infections in the hope of influencing remote or general symptoms and disease must still be regarded as an experimental procedure not devoid of hazard.

Since unlearning is more difficult than learning, many teeth and tonsils will be removed and many nasal sinuses will be opened in the attempt to cure lesions due to vasospasm. Such therapy is nonspecific and is the equivalent of parenteral foreign protein therapy

HERPES ZOSTER OPHTHALMICUS CONSIDERED AS A VASOSPASTIC DISEASE

During the past twenty years, I have come to the conclusion that herpes zoster ophthalmicus is similar to acute retrobulbar neuritis, the principal difference being that in the former the vascular lesion is located in a sensory ganglion (the Gasserian) and involves nerve cells while in the latter it is due to an acute vascular catastrophe in the optic nerve and involves only nerve fibres. In most instances, cases of acute retrobulbar neuritis regain normal or useful vision rapidly when treated only with vaso-

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vascular instability should be considered, a concept which receives support from the fact that persons with an angiospastic diathesis have repeated attacks of the same lesion. The occurrence of the same angiospastic lesion in several patients at the same time in the spring or fall, when the daily fluctuations in the weather are most marked, explains the importance of changes in the atmospheric environment *in the precipitation of disease.*

This chapter opened with a quotation from Hippocrates. It is appropriate to end it with a quotation from Petersen.

"We are accustomed to regard the blood supply to the tissues as uniformly adequate unless gross pathologic disturbances exist. . . . clinically we seldom consider the possibility of regional or organ inadequacy of vascular function unless the clinical manifestations are obvious, as in Raynaud's disease or related disturbances.

"As a matter of fact, variation in the oxygen supply to the tissues is probably one of the most common of events, and dysfunction and inadequacy of the mechanism that has to do with oxygen supply are probably the fundamental causes of disease."

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2

Vasospasm and Skin Diseases

By

Frederick R. Schmidt

The smallest arteries and arterioles of the skin contract and relax in response to stimuli of exogenous and endogenous origin. Before considering these reactions of spasm and dilatation, the main anatomic features of the cutaneous blood vessels will be briefly reviewed.

The arterioles enter the skin from a system of larger vessels comprising a meshwork situated at the junction of the subcutaneous tissue and dermis. They then pass up to the horizontal meshwork in the subpapillary layer in such a manner that cones of dermal tissue are formed, the bases of which lie against the epidermis.

The precapillaries and capillaries arise from arterioles in the subpapillary meshwork and continue as minute cylindrical tubes composed of one layer of endothelial cells Each capillary leaves the subpapillary meshwork to describe a loop and then returns to end in the commencing veins which consist of a network of ven ules uniting to form veins. The capillaries and venules together may conveniently be called the minute vessels.

The capillary is usually surrounded by a few histiocytes, mast cells, and an occasional cell of the type called pericyte, which is probably a modified smooth muscle cell capable of contraction. The mast cells contain granules which secrete hyaluronic acid and heparin.

The glomus is an exception to the normal continuity of the cutaneous blood vessels, since it consists of an arteriole which connects directly with a venule without the interposition of a capillary

Since the movement of the blood within the blood vessels is governed by those physical laws that govern the flow of liquids in any other closed system of narrow tubes, it follows that the frictional resistance offered by the relatively enormous peripheral arteriolar bed is sufficient to retard greatly the rate of flow through the capillaries The intracapillary pressure drops to zero, and the rate of blood flow through the capillary bed is slowed something like several hundred times. The slow passage of blood through a capillary's 1 mm. of length is physiologically necessary to allow time for the normal exchange of gases, electrolytes, crystalloids, and waste products of metabolism between the plasma and the interstitial fluids.

The cutaneous arterioles and minute vessels are important components of the peripheral vascular bed which comprises the blood vessels of the skin, brain, kidneys, muscles, and special sense organs. These vessels are end vessels and do not have free anastomotic connections as do those of the splanchnic areas which anastomize freely to nourish the liver spleen, and intestine The body has, therefore two large reservoirs of blood the peripheral and the splanchnic. Spasm of the splanchnic vessels results in a rise in blood pressure and in the expulsion of a large part of the splenic blood volume The blood volume immediately shifts to the peripheral bed, chiefly where the arterioles and minute vessels have become dilated through the mechanism of the axon reflex which will be considered later This shift of blood between the splanchnic and peripheral vascular beds is constantly necessary to meet such ordinary demands of everyday life as exercise weather changes, emotional stresses, and injury

The arterioles of the peripheral system all react in a like manner to spastic impulses set up by different kinds of stimuli. Similarly spastic impulses transmitted to the splanchnic area induce spasm of all the arterioles of the splanchnic system. This similarity of vascular response within each of these two vascular systems is correlated with a similar tissue response. It has been found for instance that most patients with exfoliative dermatitis who come to autopsy also show exfoliation in other organs of the peripheral system, notably in the kidneys

These rapid shifts of blood volume between the splanchnic and peripheral vascular beds are impossible to pin down with chemically fixed sections. The newer staining methods applied to fresh, frozen-dried skin specimens likewise fail to show dynamic episodes of vasospasm. The changes usually observed beneath the microscope are those associated with the compensating phase of dilatation which always follows vasospasm, and the observer is naturally a little skeptical about the ill effects of vasospasm when all he sees is dilated capillaries. This holds true for neurodermatitis as well as for dermatomyositis, lupus erythematosus, cutaneous sarcoidosis, acrosclerosis, and other disorders whose early stages are associated with episodes of arteriolar spasm.

It is often possible to establish the tone of the arteriole and minute vessels by observation of the cutaneous lesions. In psoriasis, a small, pale halo can often be seen encircling some of the small, fresh papules. The halo expresses the increased tone of the minute vessels. On the other hand, the bluish halo and the lilac ring surrounding many fresh lesions of sarcoidosis and scleroderma, respectively reflect the decreased tone of the minute vessels.

The capillary microscopic examination in the early phases of both acute disseminated and chronic discoid lupus erythematosus shows that changes occurring in the blood and lymphatic vessels of the dermis are the earliest demonstrable histoanatomic alterations. The dynamic initial phase of vasospasm, however is not only of short duration, but it is difficult to detect with the capillary microscope, because it is limited to arterioles lying at a low level in the dermis.

To overcome this difficulty Graham used other methods to determine the tone of the arteriole and minute vessels. These included a Hardy radiometer and a weighted ring applied to the skin to measure the reactive hyperemia threshold. Huff recently found evidence of a vascular dysfunction in patients with psoriasis, scleroderma, and lupus erythematosus

The innervation of cutaneous blood vessels is accomplished chiefly by fibers of the sympathetic nervous system. An environmental stimulus sets up impulses in the hypothalamus and medullary vasomotor centers, which course along these fibers to produce

sweating, pilomotor reaction, and peripheral vasospasm. These reactions of general excitation of the sympathetic nervous system are mediated by epinephrine and norepinephrine. The latter acts at the nerve endings *on the arteriole to produce vasospasm* with its clinical expression of blanching of the skin. Although subendothelial dilator fibers are included in the sympathetic fibers of the arteriole and precapillary actual dilatation of these vessels is brought about for the most part through the medium of the axon reflex.

The axon reflex is effected by the arc formed by the division of the terminal nerve filaments into two branches. One limb contains afferent fibers which end in a cutaneous structure such as the hair papilla, while the other limb has efferent fibers which end in numerous ramifications that cross each other to form a delicate meshwork encircling the arteriole. A stimulus applied to the skin sets up impulses that travel centrally over the path of the afferent fibers to the point of division of the nerve into two branches. At this point, instead of continuing on centrally to the vasomotor center they are reflected down the other branch to the nerve ending of an effector organ.

These impulses diverted from their normal journey to the vasomotor center bring about vasodilatation through the liberation of *acetylcholine at the nerve endings on the arteriole. For this reason*, dilator impulses and stimuli are known as cholinergic.

Were it not for the axon reflex, vascular adjustments to meet the demands of tissue activity would not be possible. For example a man taking a long cross-country walk to which he is not accustomed would soon be unable to continue walking because the increased hydrogen ion concentration of the blood, produced by *the metabolites carbon dioxide and lactic acid in the muscle* and acting on the medullary vasomotor centers, would send spastic impulses to his muscles and soon render them ischemic and incapable of concentration The increased hydrogen ion concentration of the blood simultaneously brings about spasm of the splanchnic arterioles through stimulation of the vasomotor center

Through the mediation of the axon reflex, the residue of carbon dioxide and lactic acid which does not enter the blood stream induces vasodilatation in the muscle and skin. The local dilator im-

pulses which are stronger than the centrally induced spastic impulses cause the blood vessels of the muscle and skin to dilate, and thus they are ready to receive the blood volume expelled from the splanchnic bed by the spasm of the splanchnic vessels.

The man finishes his cross-country walk feeling no other ill effects than pain in the muscles due to tension on the vascular walls caused by the sudden increase of blood volume.

The protective nature of vasodilatation is emphasized in a recent study by Bilisoly Goodell, and Wolff These investigators showed that the induction of vasodilatation by stimulation of the peripheral nervous system (through the mediation of the axon reflex) enhances local inflammatory processes and thus "protects the whole organism at the cost of the integrity of a part."

Although of less importance in the production of vasodilatation than the axon reflex, primary vasodilatation may be induced by direct stimulation of the subendothelial sympathetic dilator fibers of the arteriole and precapillary The result of excitation of these fibers is similar to that following regional sympathectomy with vasodilatation, hyperemia, and suppression of itching and pain.

Before ending this brief review of the mechanism of vascular reactions, another contribution to its understanding made by Petersen should be mentioned. This is the concept of two types of individuals, each reacting in his own peculiar way to environmental stimuli. The first type is the leptosome—tall, thin, wiry and nervous. His thyroid is often overactive. He is generally quick to grasp an idea, but he tires of it easily and looks around for something else. He has sweaty hands and very often, goose flesh. As an adolescent and young man he is liable to contract tuberculosis. He always seems to have a running nose. If he survives these years of frequent colds and more serious infections, he generally lives to old age.

The leptosome has an unstable autonomic system, and he responds abnormally and excessively to the impact of weather changes and emotional stresses. The patient with neurodermatitis is frequently of this type. He is unable to make the normal vascular adjustments to the stresses of everyday life because of autonomic unbalance. Spastic and dilator reactions in the splanchnic and peripheral vascular beds do not take place normally so

sweating, pilomotor reaction, and peripheral vasospasm. These reactions of general excitation of the sympathetic nervous system are mediated by epinephrine and norepinephrine. The latter acts at the nerve endings on the arteriole to produce vasospasm with its clinical expression of blanching of the skin. Although subendothelial dilator fibers are included in the sympathetic fibers of the arteriole and precapillary actual dilatation of these vessels is brought about for the most part through the medium of the axon reflex.

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From this it is evident that excitation of the sympathetic nerves to the skin, induced by an environmental stimulus, leads simultaneously to the release of norepinephrine which produces arteriolar spasm and to the liberation of acetylcholine at the sweat gland, which causes sweating. This is reflected clinically in the general pallor of the skin and the cold, sweaty hands of neurodermatitis patients.

Cold, clammy feet in patients with nodular vasculitis are likewise due to the sluggish circulation brought on by the alternating rhythm of vasospasm and dilatation. This disorder and stasis dermatitis are always associated with some type of vascular disturbance.

When the skin of most normal individuals is lightly stroked by the fingernail, a white line forms immediately This white reaction is an expression of the increased tone of the minute vessels and is reflected clinically by pallor of the skin. If the pressure on the skin is increased as with scratching, the skin grows red and warm, because the arterioles become dilated as a result of antidromic impulses transmitted along the path of the axon reflex, the minute vessels becoming atonic at the same time. If the stimulus applied to the skin is still heavier or frequently repeated, a larger area of redness appears which is called the flare.

The red reaction and flare are associated with the presence of histamine or a diffusible histaminelike substance liberated from epidermal cells The flare is therefore a normal response to histamine or injury and is an expression of full arteriolar dilatation and capillary atony

The same stimuli, however applied to patients with neurodermatitis usually effect a white line instead of the flare. The mechanism whereby this abnormal response occurs is being currently studied.

The most dramatic effect of arteriolar spasm on the perivascular tissues and interstitial fluids is partial oxygen want which is reflected clinically as a cool skin. If the minute vessels are simultaneously constricted as is usually the case at the beginning of arteriolar spasm, the skin is also pale. Since most cutaneous vessels resemble those of the entire peripheral bed in having poor anastomotic connections with a relatively small potential capillary sur

face, an oxygen deficiency in vessels distal to the spastic arteriole may be precarious to the cutaneous structure supplied by that particular vessel.

Some years ago I tried to gain an insight into the fate of cutaneous oxygen and the manner in which it is distributed. These studies were carried out previous to the use of fresh, frozen-dried sections and before accurate methods of cutaneous oxygen determination were available. The information obtained from these studies, however was sufficiently clear to indicate that the dermis enclosed within the triangles and trapeziums of dermal tissue lying between the arterioles as they continue on up to the subpapillary meshwork is normally deficient in oxygen. These areas are inadequately supplied with blood vesels and can easily be thrown into a phase of oxygen want at times of increased tissue activity

Demand for oxygen was found greater in hairy skin, as on the extensor surfaces of the extremities The extensor surfaces are exposed to a good deal of injury the friction of clothes rubbing on the hairs and insults of every nature falling more readily on them than on flexor areas. It will also be recalled that lightly stroking the skin with the fingernail is sufficient to provoke capillary contraction. In view of all this it is evident that available oxygen is scarcer in extensor areas than in flexor areas. This probably plays an important part in the predilection of certain dermatoses for the extensor areas.

I also found detectible differences in the skin temperature of different areas, notably in the skin of the extremities. Skin temperature is regulated by the arteriolar tone and the glomus. The average temperature on flexor areas was 0.2 C. higher than on corresponding extensor surfaces, which means that the rate of blood flow through the former areas is greater than through the latter and that consequently the flexor areas contain more oxygen than the extensor areas.

A brief review of what happens to oxygen after it reaches the skin will emphasize its importance to cutaneous vitality Many cell metabolites are oxidizable substances living cells must therefore contain oxidizing agents of some kind capable of oxidizing these substances These agents are enzymes contained within the

mitochondria, they are members of catalytic systems, not only controlling the oxidation of metabolites but also the liberation of energy

Cytochrome is one of these enzymes It is a hemic compound of protein with complexes of porphyrin and iron and is widely distributed in nature. The highly aerobic bacteria, for instance, usually have all the components of the cytochrome system which includes cytochrome a, b, c, and cytochrome oxidase. Mycobacterium leprae, however is an exception in that it is deficient in cytochrome oxidase.

The over-all function of cytochrome is to mediate between two catalytic systems. It is the link between the opposing systems composed of molecular oxygen and cytochrome oxidase on the one hand, and that of the dehydrogenases on the other An active oxygen-cytochrome oxidase system is essential to the transport of hydrogen which is removed during the oxidation of the substrate. Cytochrome is also concerned in the oxidation of inter mediate metabolites to melanin.

A discussion of the relationship of vitamins, proteins and metals to the oxidative catalysts will be found in the section devoted to the deficiency (nutritional) dermatoses

The impact of vasospasm on the skin is reflected clinically by blanching. As the rebound of dilatation sets in following the spastic episode, the arterioles and minute vessels become dilated and atonic. The skin reflects the dilated state of these vessels by becoming red and warm. In vascular headache of the migraine type, Wolff, Tunis and Goodell showed that headache is the clinical expression of vasodilatation which I believe always follows an initial phase of spasm of the blood vessels. In the same way the painful muscles of the man who took a long cross-country walk reflected the dilated state of the small peripheral blood vessels.

As a result of vasodilatation, the capillary becomes more permeable and allows certain particulate matter to enter the perivascular tissues. In all three types of transudation described by Duggan, fluids are the first to penetrate the perivascular tissues. In more severe grades of transudation, the fluids are soon followed by proteins and colloids and finally by red blood

cells and bacteria. This results in the formation of edema and infiltrates of blood elements and bacteria with subsequent liquefaction degeneration and possible cellular invasion of the basal cell layer of the epidermis. The interstitial fluids fill with water soluble colloids which raise the osmotic pressure, resulting in the withdrawal of water from the intracapillary plasma protein.

The edema formed in this manner is a striking feature of the early erythematous phase of lupus erythematosus. The water soluble colloids in this edematous fluid may prove to be responsible for the subsequent degenerative changes of the nucleic acid molecule contained particularly in the ground substance, collagenous fibers, and ground substance of the epidermal-dermal membrane and basement membrane of the small blood vessels in acute disseminated lupus erythematosus

The histoanatomic changes observed in many of the "collagen diseases" are therefore secondary to spasm and dilatation of the small blood vessels, which are the earliest demonstrable evidence of the disorder furnished by capillary and histologic microscopy

This pathogenic concept receives support from the demonstrated mode of action of corticotropin and cortisone. It has been shown that the protective covering of these agents, thrown around the connective tissue basement membrane of the arterioles and the capillary endothelium, abolishes the destructive reactions which are the customary result of inflammation, whether produced by physical, allergic, bacterial, viral, toxic, or other environmental stimuli. I believe that this protective covering also prevents the water-soluble colloids which have escaped from the dilated small blood vessels from diffusing into the interstitial fluids. In this way the subsequent formation of fibrinoid and sclerosis may be prevented.

Williams recently demonstrated in animals that the transudation of leukocytes with subsequent exudate formation can be reduced by cortisone therapy He also showed that the adrenocortical steroids are capable of altering the reactivity of small blood vessels to a variety of inflammatory stimuli.

The presence of bacteria in the perivascular tissues is therefore brought about by vasodilatation. Like colloids they wander through the swollen endothelial membrane of the dilated capil-

lary Nedzel's photographs of sacrificed animals in which he had induced vasospasm show streptococci or typhoid bacilli adhering to the swollen endothelial lining and passing through gaps between the endothelial cells into the perivascular fluids

The picture of streptococci clinging to the endothelial lining of blood vessels is reminiscent of that observed in the rickettsial fevers, diffuse necrotizing lepromatous leprosy bartonellosis and meningococcemia, in which the causative agents of these disorders are found in the walls of the small blood vessels of the skin. Rickettsiae have been demonstrated in and about the endothelial cells of arterioles and capillaries in material taken from patients with classic typhus fever Rocky Mountain spotted fever and scrub typhus and Bartonellae bacilliformes in both the hemic and verrugoid phases of bartonellosis.

In histologic sections of fresh lesions in the acute phase of diffuse necrotizing lepromatous leprosy the blood vessels of the dermis are seen surrounded by an inflammatory infiltrate. The endothelial cells are swollen, and many not only have M. leprae adhering to them, but they also contain large masses of bacilli which balloon them out. In this early phase no bacilli are found either in the perivascular cells or interstitial fluids.

THE WEATHER AS A CAUSE OF VASOSPASM IN SKIN DISEASES

In order to evaluate Petersen's concept of the weather as the principal cause of vasospasm, it should be recalled that arteriolar spasm exerts its influence on the oxidation reduction potential through the mediation of the catalytic system of respiratory enzymes. As I pointed out earlier the function of these enzymes depends on the oxygen supply of the cell, and the amount of oxygen available at the cellular level is regulated mainly by the tone of the smallest arteries and arterioles.

The following pages are devoted to some of the clinical and experimental evidence showing that the weather is an important factor in the production and aggravation of certain skin diseases and that it is one of the chief causes of vasospasm.

I have before me two letters typical of others received over a period of 30 years. The first is from a young woman living in Arizona, who left Chicago on my recommendation to secure

proximity of the snow-covered Andes. The cooling effect of the Andean snows upon the atmosphere of Santiago produces great diurnal fluctuations of barometric pressure and temperature. A drop of 30 or 40 F between the afternoon and early morning hours is an almost daily occurrence for weeks at a time. The daily impact of such a great fall in temperature and rise in barometric pressure, induced by the influx of cold, heavy air from the mountains, leads to severe episodes of vasospasm, the sequelae of which are of primary importance in the production of disorders of the peripheral vascular system, such as lupus erythematosus, headache coronary disease, and choroiditis.

The vasomotor center is stimulated directly by the cooled blood and reflexly by the cooled skin and nasal mucosa. The unopposed spastic impulses set up in the vasomotor center in this manner then bring about spasm of the peripheral blood vessels, which is immediately followed by the compensating acts of dilatation and atony

It was shown that such dilated and atonic capillaries become permeable to various substances of which water in the plasma proteins is an important one. The mechanism of the migration of water from the blood to the interstitial fluids of the mucous membranes and skin during exposure to cold air is therefore the same as that of the loss of water from the blood when ice is applied directly to the skin, the explanation of the congestion in both instances lying in vasospasm and its rebound of vasodilatation.

My studies on the relationship of the weather to skin diseases indicate that in many instances there is a definite correlation between the occurrence of a sudden drop in temperature with concomitant rise in barometric pressure and the onset of the dermatosis. Hair began to fall out in the majority of patients with alopecia areata, and symptoms appeared in most patients with herpes zoster psoriasis pityriasis rosea, ulcus vulvae acutum, and erythema multiforme at the time of or just after a typical polar infall. Clinical episodes also occurred in patients hospitalized for diseases of the eye and ear on the day of the polar infall, when there was a sudden upturn of barometric pressure and an equally rapid fall in temperature. This observation points to the

close relationship of vascular reactions in the tissues of the peripheral system.

In the report of these studies published in 1935 I noted the association of peptic ulcer with psoriasis in one of my patients. This patient, a 42-year old white man, had suffered from peptic ulcer and psoriasis for many years. "Early in the morning of January 5, 1935, he was awakened by a severe cramp with abdominal distention. He had not deviated from his usual simple diet. During the next forty-eight hours, the psoriasis became markedly worse." The meteorogram of that day showed that the clinical episode occurred at the onset of a severe polar infall which was accompanied by a sharp rise in barometric pressure and a drop in temperature.

This observation confirms Petersen's concept of the importance of the weather in the precipitation of not only episodes of peptic ulcer and psoriasis but of disease in general. Unfortunately the complacency of physicians concerning the meteorologic conditions as a precipitating factor in disease continues to prevail today as it did 25 years ago when Petersen began to expound his ideas.

EMOTIONAL STRESS AS A CAUSE OF VASOSPASM

Blessed as the gods the man who sits beside you, hears you speak, and sees you smile. For me at the first sight of you, my speech fails, my tongue breaks, thin flame runs through me, my eyes are blinded, my ears tingle, a cold sweat overflows me, all my body trembles, my color goes, my very death seems coming upon me.

SAPPHO

"My color goes,— Certainly a clear indication of vasospasm induced by emotional stress. The weather and emotional stress are the chief causes of vasospasm. Cormia, in his chapter on the psychosomatic dermatoses, cites the studies of Graham and Wolf. These authors succeeded in inducing arteriolar dilatation and lessened small vessel tone following initial spasm during psychically traumatic interviews with patients with urticaria.

Ecker and Riemenschneider obtained angiographic evidence indicating that emotional stress induces contraction of the cere-

it is supplied in ampoules of 1 cc. containing 100 mg. of sodium nitrite in a saline phosphate solution. The injections should be given slowly particularly the first one. An uncommon side effect is syncope for which inhalations of aromatic spirits of ammonia are an effective antidote.

The intravenous use of procaine hydrochloride or calcium gluconate usually induces vasodilatation. The vasodilating effect of intravenous procaine may be ascribed to stimulation of the subendothelial sympathetic dilator fibers of the small blood vessels. *This is not the same as saying that procaine acts by* paralyzing the spastic fibers a concept that is still championed by many physiologists.

At the time of my report on the use of oral procaine, I made *use of the Thorn test to establish a possible relationship if any* between the action of vasodilators and that of corticotropin and cortisone. The results showed that procaine exerts its influence independently of adrenocortical stimulation.

Effective vasodilator therapy requires prompt institution in the early phase of the disease. Large doses should be used, these to be doubled at high altitudes Smoking must be prohibited. Chilling is to be avoided, and the patients should avoid drafts, air-conditioned rooms, and strong winds. The fresh-air enthusiast should curb his ardor and sleep in a room where the temperature remains fairly constant throughout the night. Most important of all, a truce should be declared on family and business troubles. The assumption of an Olympian calm is ideal.

Adjuvant vasodilator treatment with hydrotherapy diathermy electric heating pad, light body massage, relaxation technic, and sedatives is highly indicated and should be used whenever possible.

Effective vasodilatation may be obtained by a prolonged bath. For many years I used an insulated, prolonged-flowing bath with hammock in the management of itching generalized dermatoses, such as exfoliative dermatitis psoriasis with erythroderma or arthropathy dermatitis herpetiformis, neurodermatitis, and severe instances of herpes zoster Vasodilatation resulting from such prolonged baths also brings about relaxation and relief from the sensation of a tight band around the head, a feeling shared by many persons having neurodermatitis.

The local induction of vasodilatation with substances such as iodine, silver nitrate, or phenol is relatively easy to achieve but impracticable to maintain for days at a time without running the risk of irritating the skin.

The removal of suspected allergenic substances from the environment and diet is essential, as is the removal of any focus of infection, both allergy and infection being common causes of vasospasm.

The elimination of a dietary allergen or a focus of dermatophytosis between the toes frequently leads to the clearing of an obstinate case of dermatitis of the hands. Increased irritability of the peripheral blood vessels brought about by localized antigen-antibody reactions in another area of the body can cause or prolong such a dermatitis

Petersen showed that arteriolar spasm is part of what he called the ARS phase in which A represents anabolism, R, reduction, and S spasm of arterioles or of any smooth muscle. Among the alterations accompanying the ARS phase are decreased tension of carbonic acid in the blood and relative alkalosis. Patients with vasospastic disorders such as neurodermatitis and herpes zoster are therefore instructed to drink a teaspoonful of cider vinegar in a glass of water three times daily and use an acidifying diet.

I have observed a favorable response to treatment solely with vasodilators in the following disorders

Acrosclerosis (generalized scleroderma)
Alopecia areata
Angiodermatitis
Dermatitis herpetiformis
Drug eruptions
Erythema multiforme
Erythema nodosum (idiopathic)
Herpes simplex, herpes zoster
Hypersensitivity reactions, particularly to cold in patients with angiodema or exfoliative dermatitis
Itching of legs associated with peripheral vascular disease
Lichen planus
Nodular vasculitis
Panniculitis, febrile atrophying
Pityriasis rosea

of cortisone therapy in conjunction with expert psychiatric management has failed to produce tangible results is to send him to a locality with a dry warm climate, free from sudden changes of weather and blasts of cold wind. The freedom from episodes of vasospasm afforded by such a climate is the factor that makes life bearable and relatively free from attacks of neurodermatitis, because it compensates for the vasospastic influence of whatever emotional stresses the patient may have.

To tide the patient over the first few months of adjustment, during which it is not unusual for him to have exacerbations of the disease, he should take a mild sedative daily and apply hydrocortisone acetate ointment or lotion several times daily to the itching areas.

In children up to four or five years of age, great improvement is possible by eliminating the allergic and emotional factors which are the most important causes of vasospasm and neurodermatitis in infancy and early childhood. In my experience, food allergy is a rare factor in the aggravation of neurodermatitis in adults.

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3

The "Collagen Diseases"

By
Jorge Abulafia

THE CONNECTIVE tissue was regarded until recent times as an element of support and a conductor of nutrient vessels, serving to bind together the various structures of the body. The work of Klinge and that of Klemperer, Pollack, and Baehr showed that disturbances of the normal regulatory controls of the connective tissue play an important and dynamic part in the production of many different disorders.

Klemperer pointed out that these disorders of the connective tissue system were not necessarily associated with each other except for the similarity in histoanatomic changes, particularly of the extracellular elements. These disorders may arise primarily without previous tissue changes or secondarily in association with peptic ulcers, pyogenic infections, or foreign-body reactions.

The group of disorders showing primary involvement of the connective tissues was originally composed of disseminated lupus erythematosus, periarteritis nodosa, rheumatic fever, rheumatoid arthritis, generalized scleroderma, and dermatomyositis, all of which may be designated as the "diffuse collagen diseases."

The unhappy term "collagen disease" is due to the concept held by early investigators that the ground substance represents the product of degenerated collagen bundles. Current evidence seems to indicate, however, that the ground substance and not the collagen bundles is the site of the histoanatomic changes.

This concept has made some observers unwilling to accept the fact that the connective tissue is really primarily concerned in the pathogenesis of these diseases. The connective tissue constitutes a biologic entity closely related to the blood vessels on

which it depends for its nutrition. The slightest vascular alteration, regardless of whether it is of a functional nature or associated with localized inflammatory reactions, is capable of provoking histoanatomic changes of the connective tissue, without any quantitative relation between the two processes. Accordingly the diseases of the connective tissue should embrace disorders of this character This is therefore a histopathologic concept and not a pathogenetic one.

In the enthusiasm over the discovery of the importance of the ground substance, sound principles of pathology were overlooked. This occurred in spite of the essential identity of the histologic changes in the intercellular and extracellular elements of the connective tissue. There can be no disease where there is no life therefore disease can only be found where cells exist. Further more, it should not be forgotten that the fundamental histoanatomic lesions are those of degeneration, necrosis and atrophy of the various components of the connective tissue, rather than the exclusive fibrinoid degeneration of the ground substance and the collagen bundles. By placing the emphasis on the predominance of extracellular involvement, the impression has gradually prevailed that only the extracellular elements participate in the disorder Inflammatory and vascular lesions and degenerative changes of other tissue such as the striated musculature, cartilage, and subcutaneous fat have thereby been neglected.

The prerequisite that the lesions must be generalized is also open to criticism, because this would exclude the circumscribed forms of some of these disorders from membership in this group.

The fact that the fundamental change in both the "collagen diseases and the disorders associated with reactions of hyper sensitivity is fibrinoid degeneration led Klinge and others to assume that most of the "collagen diseases" are expressions of hypersensitivity Later however it was shown that fibrinoid changes can be produced experimentally by hypertension and by mechanisms concerned in other nonallergic disorders.

Klemperer Pollack, and Baehr repeatedly stressed the multiplicity of precipitating factors in fibrinoid degeneration by stating that "to identify this system as the site of certain diseases is by no means to identify these diseases with one another or even to

relate them." In spite of this warning, physicians persist in ascribing a common pathogenesis to these diseases.

THE NORMAL CONNECTIVE TISSUE

The function of this tissue is concerned with varying types of metabolism the formation of the collagen bundles and the ground substance the regulation of the salt-and-water balance; the exchange of gaseous and particulate matter between capillaries and the interstitial fluids and the control of the processes of inflammation and tissue repair

The behavior of the connective tissue is regulated mainly by hormones, vitamins, enzymes, and nervous stimuli. It has been demonstrated, for instance, that desoxycorticosterone acetate not only increases the formation of the ground substance by stimulation of the fibroblasts but also greatly increases the permeability of certain membranes, while the cortisones suppress it. Estrogen, on the other hand, tends to increase capillary permeability Testosterone, progesterone, and estradiol inhibit the formation of collagen by acting on the pituitary gland. Thyroid hormone and vitamins A and C tend to stimulate the production of collagen bundles.

The connective tissue is composed of such cells as histiocytes, fibroblasts, fibrocytes mast cells, and extracellular elements such as the collagen bundles, ground substance, and elastic and reticulum fibers. These tissues are separated from the capillary endothelium and surface epithelium by a basement membrane consisting also of connective tissue.

The collagen bundles are made up of delicate fibrils formed by various amino acids. The fibrils are bound together in compact bundles by a homogeneous substance which is positive to the periodic acid-Schiff stain (P.A.S.) This cemented ground substance assumes a bright red color with van Gieson's stain.

The elastic fibers are made up of spiral-shaped fibrils, the *protein fraction of which consists of various hydrocarbons,* sulphuric acid, and lipids These fibers are specifically stained by orcein and fuchsin-resorcinol.

The reticulum fibers are stained black with silver stains and have a physicochemical composition similar to that of collagen.

The structural composition of the basement membranes varies. In some areas, it consists of an amorphous substance such as is found in the capillaries of renal glomeruli and Descemet's membrane. This substance is of a glucoprotein nature. In other areas, it consists of only a small amount of this amorphous substance, giving the tissue a weblike appearance.

In some types of adult connective tissue and in fetal life, these fibers are separated by spaces which are filled by amorphous primary ground substance. This is composed of mucopolysaccharides, loosely bound to small protein fractions. They imbibe colloidal iron and have metachromatic staining properties.

Three types of amorphous substance are found in the connective tissue the cemented ground substance of the collagen bundles the ground substance of the basement membranes and the interfibrillary ground substance.

HISTOPATHOLOGY OF THE CONNECTIVE TISSUE

Histoanatomic alterations of the connective tissue are found in congenital malformations metabolic disorders, reactive inflammatory infiltrates, and benign and malignant neoplasm.

It is current practice to include in the collagen diseases" only those associated with lesions of the connective tissue due to disturbances of metabolism, the basic change of which is fibrinoid degeneration. This, however is only one of many histoanatomic changes involving the connective tissue.

The histologic changes observed in these disorders are of three types; degeneration, necrosis, and atrophy

Degeneration, according to Mancini, is of two kinds. In one type, there exist alterations in the functional equilibrium between the fibers and the ground substance which are represented by mucoid degeneration, fibrosis, and sclerosis.

During fetal and early post-uterine life, an equilibrium exists between the primary ground substance and the fibers, with a slight predominance of the former Fibrillary elements gradually make their appearance and increase in number at the expense of the primary ground substance, which ultimately almost completely vanishes. By this time these elements have acquired the appearance of mature connective tissue. However a small resi-

due of amorphous substance remains to bind together the delicate fibrils which make up the collagen bundles.

Whenever this equilibrium is upset, the primary ground substance tends to reappear initiating the process of mucoid degeneration. On the other hand, an increase of fibrillary elements may occur resulting in fibrosis or sclerosis

Mucoid degeneration is characterized mainly by an increase in the number of fibroblasts and by deposits of mucin. The nuclei of the fibroblasts are swollen, and the cytoplasm has the appearance of that of immature histiocytes. The collagen bundles are thinned and diminished in number and they are separated from each other by deposits of bluish edematous mucin that is stained red by mucicarmine. The elastic fibers are thickened and degenerated, and the primary ground substance is abundantly present. Mucoid degeneration occurs in myxedema.

Depending on the type of connective tissue involved the fibrosis is either collagenous or reticular

In collagenous fibrosis, the connective tissue cells have the appearance of highly differentiated fibroblasts. The collagen bundles are thickened and the ground substance shows hyalinization. The elastic fibers are intact in some sections and absent in others. Generalized scleroderma shows this pathologic change.

In reticular fibrosis, there is an increase in the reticulum fibers at the expense of the other connective tissue elements. It is found in chronic glomerulonephritis.

Mancini s other type of degeneration found in these disorders is an alteration or disappearance of the extracellular elements of the connective tissues with replacement by material such as hyaline amyloid colloid, fibrinoid, and lipoid proteinosis.

In hyaline degeneration, one sees deposits of a homogeneous substance which stains bright red with eosin. Hyaline is the product of degenerated collagen and reticulum fibers and is found mainly around the small blood vessels and within the intima and media of larger vessels.

Fibrinoid degeneration is marked in early lesions by thickening of the collagen bundles which are intensely eosinophilic and color yellow with van Gieson s stain In advanced lesions silver stains show fragmentation of the collagen bundles which are inter

spersed in patches of altered ground substance. The primary ground substance is not visible. The nuclei of the fibroblasts and histiocytes are found scattered throughout the affected areas. Many of these nuclei are retracted and strongly basophilic.

In amyloid degeneration of the skin, one sees small deposits of a homogeneous material that is stained lavender by methyl rosaniline chloride and dark mahogany with Lugol's solution. It is currently regarded as consisting of proteins which are sometimes linked to chondroitin-sulphuric acid.

Amyloid is occasionally found in atypical locations such as the papillary body and subcutaneous fat, where it does not take the customary stains for amyloid. Its presence in these areas has not been satisfactorily explained. It is usually found in association with hyaline degeneration.

Colloid degeneration is the basic histoanatomic change of colloid milium, in which the elastic fibers are mainly involved. Colloid is the product of completely degenerated elastic fibers. It reacts positively to P.A.S The degenerative changes start with swelling of the fibers which are markedly basophilic. In this intermediate stage, lipids and hydrocarbons are found in the small, homogeneous masses of colloid lying adjacent to the dermal membrane in the upper dermis. Silver stains show delicate reticulum fibers surrounding these colloid deposits.

Lipoid proteinosis is characterized by the presence of lipid droplets in the ground substance of the dermal membrane and basement membrane of the blood vessels. A web of reticulum fibers lies in close apposition to these membranes, the ground substance of which is strongly eosinophilic and stains yellow with van Gieson's technique. It is P.A.S positive. The collagen bundles in the affected areas are greatly attenuated, and the primary ground substance is not visible.

In necrosis, there are pyknosis and karyorrhexis of the nuclei with "nuclear dust" lying in the center of necrotic foci, associated with widespread alterations of the extracellular elements. There are four types of necrosis.

In mucoid necrosis, the "nuclear dust" is found in focal areas of necrosis, surrounded by a palisadelike arrangement of histiocytes and fibroblasts as well as lying free in the necrotic areas. A

lymphocytic infiltrate is seen around the adjacent vessels. The collagen bundles are attenuated and stain feebly The elastic fibers have disappeared Suitable stains reveal the presence of the primary ground substance, which is composed of acid mucopolysaccharides capable of being digested by hyaluronidase.

Fibrinoid necrosis is found in the subcutaneous nodules of rheumatic fever and rheumatoid arthritis and represents an advanced stage of fibrinoid degeneration. The connective tissue cells show nuclear disintegration. The elastic fibers gradually disappear and destruction of the collagen bundles is brought about by fibrinoid degeneration.

Primary ground substance cannot be demonstrated. A reactive histiocytic infiltrate and deposits of lipid droplets are found around the necrotic areas.

Necrosis with calcification is the product of massive calcification of focal areas of necrotic connective tissue. It is found in scleroderma and dermatomyositis, in which one sees small clumps of calcified cells lying within a homogeneous mass and staining positively with P.A.S In contrast with other types of necrosis, there is very little perifocal histiocytic reaction, and the collagen bundles are gelled.

Necrosis with lipid imbibition is well illustrated in necrobiosis lipoidica diabeticorum The necrotic changes in this disease occur deep in the dermis where one sees deposits of lipid droplets within the degenerated collagen bundles and in some of the connective tissue cells Obliterative inflammatory changes are usually marked.

Caseation necrosis is not being considered here because it occurs exclusively in inflammatory exudates.

Atrophy is usually the result of decrease in the size and number of the collagen bundles Although the elastic fibers are usually present and intact they are occasionally absent.

THE GENERALIZED "COLLAGEN DISEASES"

The histologic appearance of the skin in acute disseminated lupus erythematosus depends on the age of the lesion, sometimes resembling that of subacute lupus erythematosus and at other

times that of the chronic discoid form of the disorder Atypical microscopic pictures are occasionally found.

Material obtained from the hemorrhagic papules on the back of the hands and fingers shows to good advantage the early inflammatory changes of the disorder The reaction is most intense in and around the dilated, edematous capillaries of the upper dermis, where many of the capillary walls have ruptured and allowed red blood cells to pass into the perivascular tissues. The papillae are edematous, and the connective tissue cells are swollen, discharging "nuclear dust into the surrounding area. The collagen bundles become fragmented and the elastic fibers disintegrated. Small conglomerates of primary ground substance and foci of a dense perivascular infiltrate almost completely fill the middle third of the dermis in older lesions The epidermis is not involved.

Biopsy sections from other areas of affected skin may show a normal or atrophic epidermis, with flattening and liquefaction degeneration of the basal cell layer The edema may be severe enough to form intraepidermal vesicles. Fibrinoid degeneration was rarely encountered in my material.

Visceral lesions of material obtained at autopsy show marked vascular involvement. Baehr Klemperer and Schifrin, in a series of 23 autopsies, found that almost all sections showed dilated, engorged capillaries, extravasation of red blood cells, proliferative and obliterative changes of the walls of the arterioles and minute vessels, and necrotic foci in some of the vessels. The "wire-loop lesions of the renal glomeruli are caused by thickening and degeneration of the basement membrane of the glomerular capillaries. This concept of primary involvement of the vascular system is supported by the experiments of Jarcho

In a later work, Klemperer Pollack and Baehr showed that the primary lesions arise in the connective tissue. Fibroblasts showed proliferation, degeneration, and even necrosis. The fundamental lesion of the intercellular elements was fibrinoid degeneration, usually associated with sclerosis. The pericardium, endocardium, and the connective tissue of the myocardium, kidneys, spleen, and skin participated vigorously in the general disorder "Wire-

loop" lesions or foci of necrosis were found in the renal glomeruli. The spleen showed marked fibrosis around the central arteries.

An analysis of these histopathologic findings indicates that the lesions of acute disseminated lupus erythematosus are limited to the blood vessels and the connective tissue.

The possibility that the arterioles and minute vessels of the peripheral vascular bed, notably those of the skin and kidneys, are the first to react to a hypothetical circulating infectious or allergic agent should be considered. According to this concept, arteriolar spasm and its rebound of dilatation, with the production of increased permeability precede the involvement of the ground substance If this is the case in lupus erythematosus, the degeneration of the collagen is pathogenetically secondary to an initial vascular involvement, as it is in some of the other generalized "collagen diseases" From a histopathologic standpoint, however the occurrence of predominantly fundamental lesions of the visceral connective tissue allows us to integrate this disorder in the diseases of the connective tissue. Nevertheless it must be admitted that a study of the cutaneous lesions reveals an intense perivascular inflammatory reaction with secondary alterations of the connective tissue.

Periarteritis nodosa is characterized by polyneuritis, fever symptoms of visceral disease and hypertension I agree with Zeek in deploring the tendency to lump together under this heading all diseases having similar histologic changes but different pathogenetic factors. She mentions five types of necrotizing arteritis each of which is induced by a different etiologic agent.

The basic histoanatomic changes in periarteritis nodosa occur mainly in the arteries and arterioles of the muscles, the striated musculature, and the peripheral nerves Lesions in different stages of development are present at the same time.

In early cutaneous lesions, the walls of the arterioles at and below the border of the dermis and subcutaneous fat show focal areas of fibrinoid necrosis not infrequently associated with edema and swelling of the capillary endothelium. Segments of the intima and media become necrotic, resulting eventually in thrombosis of the lumen of affected vessels.

The vascular lesions evoke a dense inflammatory infiltrate consisting predominantly of polymorphonuclear leukocytes, eosinophils, lymphocytes and plasma cells. The disintegration of elastic fibers and the necrosis of muscle bundles also result from anoxia brought on by the interference with the blood supply caused by the obliterated vessels. The lymphocytic infiltrate is finally replaced by scar tissue.

Periarteritis nodosa thus begins with degeneration and necrosis of the walls of the blood vessels and is followed by widespread inflammatory reactions.

The subcutaneous nodules found in rheumatic fever consist of a central zone of fibrinoid degeneration surrounded by edematous foci of connective tissue, infiltrated with histiocytes, fibroblasts and inflammatory cells.

Reviewing the histoanatomic changes in the skin and viscera, it becomes clear that the target in rheumatic fever is the connective tissue. Fibrinoid necrosis is the fundamental lesion, along with inflammatory reactions of the capillary endothelium.

The histologic changes differ from those in disseminated lupus erythematosus by the presence of extensive cellular reactions in and around the focal areas of fibrinoid degeneration, the lesser tendency of the lesions to become generalized, and the absence of renal involvement.

In rheumatoid arthritis, the subcutaneous and cutaneous nodules occurring around the joints are similar to those of rheumatic fever except for the absence of edema. On histologic examination, one also sees focal inflammatory reactions in the walls of the blood vessels and degeneration of the connective tissue and cartilage.

Generalized scleroderma occurs in two forms acrosclerosis and scleredema adultorum.

In acrosclerosis, the skin is primarily affected. In very early lesions of the hands, the changes are those of Raynaud's disease, with predominance of vascular involvement. Alterations of the extracellular elements of the connective tissue gradually supervene with ultimate widespread participation of the reticular layer of the dermis. The collagen bundles become thickened and homogeneous, and they stain indifferently because the ground sub-

stance is increased in amount. There is no evidence of the primary ground substance. The elastic fibers are usually intact, or they may show focal areas of fibrinoid degeneration. The endothelial cells of the blood vessels are swollen, and there is fibrosis of the perivascular tissues with circumscribed areas of a lymphocytic infiltrate extending into the adjacent connective tissue elements. Deposits of calcified necrotic material are occasionally seen in the dermis.

A discussion of the histoanatomic lesions of visceral scleroderma does not fall within the purview of this section.

Scleredema adultorum is an abortive form of scleroderma which may go on to become the generalized form of the disorder

In the skin, the swollen collagen bundles are widely separated from each other by the intense edema which often produces large unstained spaces. Freund and Vallee reported the occasional presence of a metachromatic-staining substance with small areas of perivascular inflammatory infiltrate

Dermatomyositis is mainly characterized by involvement of the skin and skeletal musculature. The disease also affects the heart, subcutaneous fat lungs, liver kidneys and blood vessels.

In the skin, the histologic changes in early lesions are often not typical. More advanced lesions, however show atrophy of the epidermis with liquefaction degeneration of the basal cells. The dermis, particularly in its upper third, shows mucoid degeneration and edema, especially around the blood vessels. A moderately severe infiltrate, composed predominantly of lymphocytes, plasma cells, and eosinophils, lies in the dermis around the capillaries and cutaneous appendages. In older lesions, the dermis may be atrophic· usually however it appears broader than normal in relation to the shrunken degenerated subcutaneous tissue The ground substance disappears, being replaced by fibrosis similar to that in scleroderma. Both the dermis and subcutaneous fat may show areas of necrosis and calcification.

The skeletal muscles and occasionally the striated muscles of the larynx and esophagus show hyaline and vacuolar degeneration and invasion of the muscle bundles by lymphocytes and at times polymorphonuclear leukocytes Although sometimes there is a mild inflammatory reaction of the connective tissue at other

times in spite of widespread parenchymatous degeneration of the muscle bundles, there is little or no involvement of the connective tissue.

The small blood vessels may show slight swelling of the endothelial cells or more severe changes, such as hyalinization of the intima and obliteration of the lumen by thrombosis.

The histologic findings in dermatomyositis are those of a true "collagen disease," since the connective tissue usually participates in the degenerative changes, although to a much lesser extent than in other "collagen diseases."

THE CIRCUMSCRIBED "COLLAGEN DISEASES"

There is another group of disorders of the connective tissues less widespread in their distribution than the foregoing classic generalized collagen diseases" which show nevertheless, similar histoanatomic changes. I shall restrict myself to a brief description of their cutaneous aspect.

The upper dermis in granuloma annulare shows focal areas of degeneration or necrosis. These areas are surrounded by a palisadelike arrangement of epithelioid cells containing lipids. One also sees focal areas of edema, lymphocytes, fibroblasts, histiocytes, and epithelioid cells throughout the dermis. The blood vessels are surrounded by a zone of lymphocytic infiltrate.

Necrobiosis lipoidica diabeticorum is marked histologically by areas of degenerated and necrotic connective tissue in the lower two thirds of the dermis. One sees lipid deposits associated with increased numbers of fibroblasts, often lying adjacent to the blood vessels, many of which show obliterative changes. The collagen bundles are swollen and fused into broad sheets of compact tissue resembling that of scleroderma. Older lesions usually show sclerosis of the perivascular connective tissue with small conglomerates of foreign-body giant cells

The lipids consist mainly of free cholesterol and phospholipids.

In lipoid proteinosis, the shrunken collagen bundles of the upper dermis run perpendicular to the epidermis. The normal tissue of the dermal membrane and basement membrane of the blood vessels is replaced by a thickened, frayed zone of material having the appearance of hyaline. Particularly around the blood

vessels, one sees deposits of extracellular lipid droplets. The lipids stain a darker red with Sudan IV than those in xanthomas.

Amyloidosis cutis is characterized in early lesions by deposits of homogeneous amyloid in the dermis, mainly around the sweat glands and small blood vessels. Later amyloid finds its way into the walls of the blood vessels, often destroying them.

Mucoid degeneration is seen in both generalized and circumscribed pretibial myxedema, the latter disorder showing the largest deposits of mucin.

In colloid milium one sees severely degenerated elastic fibers in association with conglomerates of homogenous colloid lying particularly around the subpapillary blood vessels. Colloid milium is usually found associated with manifestations of porphyria.

The cutaneous porphyrias show thickening of the dermal membrane and basement membrane of the papillary and subpapillary blood vessels. The ground substance of these degenerated membranes shows a positive reaction to P.A.S. The collagen and elastic fibers show varying grades of degenerative changes. Borda, Grayeb, and Stringa reported several cases of porphyria associated with the clinical picture of scleroderma and dermatomyositis.

In circumscribed scleroderma, the entire dermis or only its middle or lower third may be involved. Occasionally only the subcutaneous tissue is affected. The appearance of these areas resembles that of generalized scleroderma. The elastic fibers tend to disappear as the process extends to the papillary body and subcutaneous tissue.

Lichen sclerosus et atrophicus is in my opinion a variant of morphea limited to the papillary layer of the dermis.

Necrotizing angiitis is produced by a number of hypersensitivity agents. Zeek has shown that it can be caused by hypersensitivity to sera or drugs. The histoanatomic changes involve predominantly the arterioles, capillaries and venules of the kidneys, lungs, and spleen. All the lesions are in the same stage of development. The histologic picture resembles that of periarteritis nodosa.

The triple-symptom disease of Gougerot is characterized by focal areas of fibrinoid necrosis within the thickened walls of the small arterioles and capillaries. An inflammatory infiltrate of lymphocytes, histiocytes plasma cells, and eosinophils is found around these vessels, along with a few red blood cells.

In idiopathic atrophoderma of Pasini there is atrophy of the collagen bundles, with reduction in their number The elastic fibers are only slightly altered.

PATHOGENESIS OF THE "COLLAGEN DISEASES"

There does not appear to be a common cause of these disorders, although there is a considerable bulk of evidence suggestive of a hypersensitivity factor in acute disseminated lupus erythematosus, rheumatic fever rheumatic arthritis and scleroderma. Some of this evidence consists of the findings of increased blood gamma globulin and fibrinoid degeneration of the connective tissue and the frequent association of foci of chronic infection or other sensitizing agents in these four disorders.

It will be recalled that elevated blood gamma globulin levels are found concomitantly not only in association with higher levels of circulating antibodies and chronic infections but also following the use of vaccines and sera. Suspicion is aroused, however that factors other than hypersensitivity play a role in the production of at least one of these disorders, lupus erythematosus, by the discovery of the L.E. cell and L.E. serum factor

The fact that the connective tissue is mainly involved in all of the collagen diseases" may explain their common clinical and histoanatomic findings, but it does not mean that they have a common etiology or pathogenesis. It is probable that different causative agents and varying host reactions evoke more or less similar clinical and histologic responses.

Although the blood in dermatomyositis does not show elevated gamma globulins, many of the clinical and histoanatomic findings are highly suggestive of an allergic etiology

This concept finds support in the frequent histories of preceding serum injections and in the presence of foci of chronic infection. Walker and Benditt reported the case of a patient with acute disseminated lupus erythematosus, in which clinical and histo-

logic findings of dermatomyositis ultimately developed, including the disappearance of increased blood gamma globulin. It is not unusual to find eosinophils in histologic sections of subcutaneous necrotic nodules.

The association of dermatomyositis occurring in women with carcinoma is by no means rare and does not mitigate against the concept of an allergic etiology. Borda found manifestations of hypersensitivity in a patient with dermatitis herpetiformis associated with carcinoma. These observations suggest that dermatomyositis *results from the exhaustion of antibody forming tissues*, caused by toxins resulting from the continuous impact of antigen on these tissues.

There are two main schools of thought regarding the cause of periarteritis nodosa. One maintains that it is a manifestation of hypersensitivity, while the other claims that it is the result of repeated episodes of hypertension.

A similar lack of unanimity in respect to pathogenesis characterizes the group of circumscribed "collagen diseases," including in addition to those mentioned previously, congenital malformations of the connective tissue determining the production of such disorders as lipoid proteinosis of Urbach and Wiethe, hormonal-induced mucoid degeneration, senile degeneration of the skin, and reactions of hypersensitivity.

SUMMARY

It is evident from all this that the concept of the identity of the "collagen diseases" rests exclusively on the histoanatomic findings.

The connective tissue responds to a variety of different stimuli with similar histoanatomic reactions. These reactions of degeneration, necrosis and atrophy may be associated with vascular lesions. An inflammatory reaction may or may not coexist. It will be recalled that the explanation of these reactions lies in the relation of the ground substance of the blood vessels to that of the extracellular elements.

The degeneration of the connective tissue developing in association with inflammatory and neoplastic diseases is secondary in nature and should not be included in the group of classic "collagen diseases."

On the basis of the data presented in this article, it seems justified to include in the diseases of the connective tissue all acute and chronic disorders, whether generalized or circumscribed, which show predominant metabolic disturbances of the connective tissue, particularly of its extracellular components. The metabolic disturbances consist mainly of degeneration, necrosis, and atrophy

It should be stressed, however that the degenerative changes of the connective tissue, especially in the generalized "collagen diseases," are often associated with lesions of other tissues such as the blood vessels, striated musculature, cartilage, and subcutaneous fat.

I would like to propose the following classification of diseases of the connective tissue, which will, I am sure, suffer considerable alteration as a consequence of future chemical and physiologic investigations of the histoanatomic changes of the connective tissue system.

DISEASES OF THE CONNECTIVE TISSUE

Congenital malformations	Pseudoxanthoma elasticum Cutis hyperelastica Lipoid proteinosis (Urbach-Wiethe) Connective tissue nevus Adenoma sebaceum
Endocrine disturbances	Generalized hypothyroid myxedema Circumscribed pretibial myxedema Necrobiosis lipoidica diabeticorum
Metabolic disorders	Porphyria Colloid milium Senile degeneration of the skin
Avitaminoses	Pellagra
Reactions of hypersensitivity	Acute disseminated lupus erythematosus Rheumatic fever Rheumatoid arthritis Generalized scleroderma Necrotizing angiitis due to hypersensitivity Triple-symptom disease (Gougerot) Granuloma annulare Amyloidosis
Toxic reactions associated with hypersensitivity	Dermatomyositis
Diseases in association with hypertension	Periarteritis nodosa
Nervous reactions	Circumscribed scleroderma following injury Idiopathic atrophoderma (Pasini)

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4

Psychosomatic Dermatoses with Specific Reference to Pruritus and Its Treatment

By
Frank E. Cormia

THE ROLE of emotional and nervous disorders in the development of pruritus and various dermatoses has recently been studied by an ever increasing number of investigators. The work of Weiss and English, and others has attempted to clarify these relationships by a simplified "psychosomatic" approach.

The methods of study used in investigations of this kind include intensive study of individual cases with a modified psychoanalytic technique; statistical analyses of disease entities by Wittkower and Russell, and me in an effort to establish uniform stress situations and psychopathologic backgrounds in specific diseases methods used by Dunbar and MacKenna in attempting to correlate personality types and individual diseases the use by Obermayer of supplementary methods such as the Rorschach test, and finally direct measurements of somatic components of the presenting symptom or entity following the deliberate introduction of psychic trauma, as advocated by Wolff and associates.

All of these techniques have added substantially to our knowledge, but objections to each have lessened to some extent their validity Among these objections is that individual case studies have been selected and therefore are not representative. Also, statistical and correlative studies are not conclusive.

MacAlpine objects to these techniques on the ground that the widely different results obtained by them are subject to great divergencies of interpretation. Sulzberger and Baer for instance, deny the existence of psychosomatic factors in acne, while Wittkower a psychiatrist, finds distorted personality pat

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clear however that tissue damage develops as a result of imperfect emergency measures evoked by the patient in dealing with adverse life situations and that this tissue damage, while of some value in the relief of tension and conflict through various mechanisms, is but rarely consciously desired by the patient. Indeed, production of injury in an effort to avoid injury is one of the great paradoxes of modern medicine. In the development of psychosomatic disease, one should consider the specific conflicts and difficulties in interpersonal relationships which operate through nervous humoral, endocrine, and other mechanisms to produce an exaggeration of a normal function such as pruritus. The continual operation of stress factors may then result in the fixation of secondary somatic changes

Seitz exemplified this psychosomatic mechanism in a study of the psychocutaneous aspects of pruritus and excoriation. In his formulation, lack of love leads to hostility which in turn evokes feelings of guilt which repress the hostile feelings. This repression then results in the evocation of a psychosomatic release in the form of pruritus. The subsequent excoriations serve a secondary purpose in that the hostility is directed on one s self as a form of punishment.

In the phobic states, Zaidens pointed out that an underlying paranoia is projected on the skin. Dermatitis factitia may be considered as a hysterical exhibitionism occurring ordinarily in middle-aged patients who have failed in life. The deeply repressed motivation includes the idea of self punishment, and the mutilating skin lesions are face-saving in that they center attention on the patient. In urticaria of psychogenic origin, there is an almost invariable background of frustration and resentment. Acute panic reactions based on fear may also produce urticaria.

In another type of experiment, I was able to show that itching due to the intradermal injection of a measured amount of histamine is often noticeably aggravated by psychic trauma induced during a stressful interview Under these circumstances, mild itching may be made severe and severe itching may eventuate into burning Furthermore, it has been possible by this means to lower the itch threshold, which is defined as the smallest amount of intradermally injected histamine which will produce itching.

In some instances it is possible to measure the intermediate phyiochemical changes concerned in the production of tissue damage resulting in psychosomatic dermatoses Kapecs and his coworkers, for instance, showed that exudation into an artificially produced bulla is often greatly increased during traumatic interviews in patients with atopic dermatitis or urticaria. The underlying mechanism involved may be concerned with the tone of small blood vessels and with extreme dilatation of arterioles. Graham and Wolf were able to demonstrate these vascular changes in psychically traumatic interviews in patients with urticaria by measurement of skin temperature and determination of the reactive hyperemia threshold. In nearly all patients studied, the reproduced traumatic life situation was associated with resentment and frustration. The deliberate production of vascular dilatation and lessened small vessel tonus during stressful interviews immeasurably expands the categories of dermatoses which may be aggravated by psychosomatic factors.

INTERPRETATIVE SIGNIFICANCE OF TYPE AND LOCATION OF PSYCHOSOMATIC MANIFESTATIONS

Although psychiatrists generally contend that psychosomatic symptoms cannot be linked with specific conflicts or life situations, I believe that there is considerable evidence to cast doubt on this contention.

Among this evidence are the observations that patients with rosacea blush easily frequently have exaggerated reactions to sunlight, are shy and easily embarrassed in tension-producing social situations Patients whose presenting symptom is itching may ignore rub or scratch their itch, depending on specific personality constellations If the response is one of continued excoriations a lichenified dermatitis will ensue. The so-called anal" type of individual more often than not gives a history of previous and frequently multiple gastrointestinal disturbances. If he then happens to develop an anal fissure or hemorrhoids, a surrounding area of itchy" skin may ensue and result in chronic pruritus ani.

PRURITUS

Since pruritus is a salient feature of most psychosomatic dermatoses, I shall briefly consider its nature and the factors influencing

its development and severity as well as its occurrence as a psychosomatic symptom.

Experimental evidence and clinical observation show that pruritus is a modified form of pain. Lewis, Grant and Marvin, and Graham and his associates have observed reciprocal relationships between itching and pain. Bishop was able to elicit itching from repeated low-intensity electrical stimulation of pain spots A painful stimulus applied during spinal anesthesia will frequently produce itching

Kuykendall and I produced itching by a burning stimulus in partially anesthetized skin. In further experiments, we were able to produce burning by the application of two to three successive itch stimuli. In some instances, irradiation of this burning site with infrared light resulted in the development of pain. These experiments indicate that itching, burning, and pain are variants of a single sensation.

It was also noted that histamine itch occurred in the presence of cutaneous flare when the wheal was inhibited by a moderate pressure from a centrally-placed tourniquet. Furthermore, the wave-like component of itching also appeared to have a vascular component associated with arterial pulsations its wavelike character disappeared when the amplitude of the arterial pulsations was diminished by moderate pressure from a tourniquet.

The mechanism of the interruption of the itch sensation, psychogenic or otherwise in character by prolonged excoriations, was clarified by a further experiment. Repeated injections of histamine in a single site produced a localized refractory period lasting up to 24 hours during this period, itching could not be elicited by further local injections of histamine. Temporary freedom from itching following prolonged excoriations in psychosomatic disorders such as pruritus vulvae or lichen simplex chronicus may thus be explained by this phenomenon of refractoriness to histamine. In these instances, further histamine is surely liberated as a result of tissue damage due to scratching

As would be expected, the character of itching varies according to the nature of the stimulus, the type of cutaneous soil stimulated, the integrity of the nerve pathways, and its perception in the somesthetic cortex. A constant amount of a standard itch stimulus such as histamine may produce a mild itch in a stable individual

and severe burning in an emotionally disturbed patient with pruritus vulvae. In some cases of itching of psychogenic origin, the sensation may take on the characteristics of pain, even in the absence of excoriations.

Kuykendall and I noted that the histamine itch threshold was greatly reduced at night. This increased reactivity to histamine confirms the well-known clinical observation that the tendency to itch is greatly increased at night. Marked increase in arterial blood flow as produced by elevation of skin temperature to 39° C., uniformly lowered the itch threshold in experimental histamine pruritus lowering the skin temperature to 25 C had the opposite effect. It may be readily understood, therefore, why increased cutaneous blood flow in an inflammatory dermatosis results in an increase in the severity of itching

It is generally recognized that conditions associated with marked edema, except for urticaria, usually are not accompanied by severe itching This situation was demonstrated experimentally by potentiating intradermal histamine reactions with the subcutaneous injection of 25 mg of metacholine. This experiment is of additional interest since it is commonly held that the response to histamine is potentiated by acetylcholine as in nettle rash. The so-called psychogenic cholinergic urticaria, therefore, must be potentiated by relatively small amounts of acetylcholine, which may explain in part the small size of the wheals in this condition.

Among the causative factors in the production of pruritus, local tissue damage is of paramount importance Histamine is liberated into the tissue in unbound form following injury Since intradermal injections of this drug generally produce itching, it is reasonable to assume that it is concerned with the itching of clinical dermatoses Itching may also be produced by direct injury of terminal pain fibrils by local cellular infiltrates, as present in lymphoblastomatous infiltrations of the skin in leukemia or Hodgkin's disease associated with severe pruritus without visible skin lesions. There is yet no adequate explanation of the severe pruritus of psychologic origin occurring in the absence of local tissue injury

CLASSIFICATION OF PRURITUS

Itching occurs in the following four general situations

1. Local inflammatory disease parasitic disease, certain systemic disorders, or psychogenic types.

2. Closely allied to the first group are itching conditions caused by the injection of urticarogenic substances by insects and deposition on the skin of irritating agents by moths and beetles.

3. Systemic conditions associated with itching are liver disease with jaundice, diabetes, uremia, the lymphoblastomas, and at times internal malignant neoplasia. The agents producing itching in jaundice and diabetes are unknown. Generalized itching is uncommon in patients with diabetes and may or may not be controlled by treatment of the diabetes Itching in patients with Hodgkin s disease often involves the lower extremities and soles, this may be caused by pressure on the nerves from retroperitoneal involvement and may respond to x ray therapy Itching in polycythemia may be benefited temporarily by treatment of the underlying condition. Generalized pruritus with or without dermatitis has occasionally been observed in conjunction with visceral carcinoma, the itching improving rapidly on removal or partial regression of the tumor Eruptions resembling dermatitis herpetiformis associated with severe itching may have a similar cause and course.

4. Psychogenic pruritus, with or without cutaneous lesions, is becoming increasingly more common. Probably 50 per cent of private patients complaining of pruritus have either psychogenic pruritus or pruritus from other causes aggravated by emotional factors. Its management depends therefore not only on intelligent treatment of any accompanying primary organic disease but also on the sympathetic understanding of the patient and his problems.

METHODS OF DIAGNOSIS AND TREATMENT OF PSYCHOSOMATIC DERMATOSES

Some years ago I began using a modified technique based on Dunbar s psychosomatic approach some 200 patients were investigated in this manner over a period of five years. The psy

Regarding parallel treatment, I believe that dermatologists may advantageously use it in the management of patients with rosacea, vesicular neurodermatitis alopecia areata, psychogenic urticaria, and some with atopic dermatitis and localized pruritus including circumscribed neurodermatitis. Patients with neurotic excoriations should be treated by dermatologists only when deep-seated emotional problems are absent.

TREATMENT OF PRURITUS

Since the background of generalized psychogenic pruritus often includes emotional instability depression, chronic anxiety and other evidences of psychoneuroses of intense grade, patients with this type of pruritus should be placed under psychiatric care unless the initial evaluation indicates that emotional problems are of minimal nature.

When the itching is more localized, as in circumscribed neurodermatitis, symptomatic suppressive treatment is generally effective, although recurrences of itching at the same or other sites are common. Such treatment includes x ray therapy the alternate use of tar and hydrocortisone ointments or occlusive dressings. The immediate response to therapy is good, but if repeated relapses occur psychiatric care may be indicated.

Kuykendall and I recently evaluated the antipruritic effects of 31 agents in the control of experimental pruritus The agents exerting a beneficial effect on the itch threshold included the antihistaminics vasodilators, nicotinamide analgesics sedatives, anticonvulsants antispasmotics, sympatholytic and parasympatholytic drugs ACTH, and cortisone. Preparations having little or no effect included calcium gluconate, bromides chloral hydrate, benadryl, and banthine. ACTH and cortisone exerted but little effect on the itch threshold, and it would seem that their well-recognized antipruritic action is due largely to the amelioration of inflammation.

It is generally accepted that hydrocortisone ointment is superior to any other single agent heretofore used in the treatment of localized itching Kuykendall and I were able to confirm the well-known effect of suggestion, by elevation of the itch threshold in some 20 per cent of patients with the administration of a placebo.

The problem of anogenital pruritus should first be carefully evaluated before local treatment is given. In general, vulvar or scrotal involvement points to disorders in the sexual realm. Both conditions may be initiated by incidental causes and then persist due to psychogenic factors. Similarly pruritus ani may be precipitated by fissures, hemorrhoids, or other local disease, but likewise may become chronic. Many of the local itching conditions when first seen by the dermatologist may be somatically fixed, and no amount of psychiatric treatment will eradicate them. Local medication is then indicated. Of the local anesthetics, I have obtained best results with Quotane Lotion. Neither Eurax nor the antihistaminics have given more than temporary relief in my experience.

*Surgical measures such as tattooing with mercuric sulfide, injec*tions of alcohol, section of the perineal nerve, undercutting of anal tissue or its piecemeal removal, and vulvectomy have had only occasional success.

The treatment of generalized pruritus with adenosine, as noted also by Pearson and Fromer has been a failure in my experience. Neither have I been able to duplicate the reported good results obtained by Beinhauer and Schmidt with procaine, except in occasional instances

THE TREATMENT OF THE PHOBIC MANIFESTATIONS, DERMATITIS FACTITIA, AND DERMATOSES WITH PSYCHOTIC STATES

I have never seen a patient with delusions of parasitosis cured of his affliction, and I have never heard of a cure obtained by psychotherapy After a thorough search for parasites has been made, the dermatologist can do little more than to reassure the patient of the innocuousness of his symptoms. The use of antipruritic or so-called antiparasitic therapy in such cases cannot be too strongly condemned.

It is my belief that there is no place for dermatologic treatment in the management of dermatitis factitia. About the only service a dermatologist can render is to obtain, if possible, the confidence of the patient and then by any means possible get him to a psychiatrist. This maneuver may have to be undertaken with the greatest guile, for the patient unconsciously wishes to retain his

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emotional traumatic or infectious stress, and climatic influences. This latter is concerned mainly with the vasodilating effect of hot weather the irritation of heavy woolen clothing in cold climates, and varying degrees of sweat retention secondary to the inflammatory process.

In my experience, all of these factors play a role in the development and persistence of the disease. However I have found that with the increasing age of the patient, the antiallergic regimens are of constantly diminishing value, while the psychotherapeutic approach becomes correspondingly more valuable.

There is a striking unanimity of opinion regarding the pathogenesis by those who have approached this problem through psy chosomatic studies My findings are fairly representative of the group. Neurotic traits are always present, and psychogenic fa milial and childhood disorders are present in 70 per cent. More than half of the patients have been subject to previous psychiatric disturbances. As Wittkower pointed out, these patients are either unwanted" or "spoiled." Overprotection by the mother and dependence frequently result in an insecure clinging patient whose behavior patterns are often of an infantile type. This leads to hostility and resentment which is frequently ventilated by sublimated social striving rather than actual aggression. The sensitiveness of these patients renders them especially susceptible to conflictual elements in their lives, and reactivity to psychic trauma is common.

I treat mild atopic dermatitis by suppressive measures, along with a common-sense, antiallergic regimen. When itching is severe, the various measures advocated for its control, including the antihistaminics, are of decided value. Cortisone therapy frequently will tide the patient over a severe exacerbation, but too much reliance should not be placed on its effects for long-term improvement. When psychogenic factors are paramount, the dermatitis may become generalized and severe despite the continued administration of cortisone. For long term suppressive effects, I prefer the use of one per cent hydrocortisone ointment.

In the milder forms of the disease, conscientious efforts by the dermatologist may right the abnormal familial situation and start the patient on the road to cure. Change of environment exerts a

three-fold effect; a high, dry climate may prevent exacerbations by the sweat retention factor the patient escapes from intolerable familial relationships and inhalant allergens may be avoided. However in severe cases, the presence of marked repercussions in personality development and interpersonal relationships calls for intensive psychiatric care in a hospital.

MISCELLANEOUS DERMATOSES

Any severe dermatitis may be aggravated by psychogenic factors, presumably on the basis of intensification of itching and subsequent to the effects of vasodilatation. Prime examples of this situation exist in acutely eczematized seborrheic dermatitis conditions of dissemination by autoeczematization, and any severe dermatitis. Treatment resistant seborrheic dermatitis occurs in tense, overworked individuals who have an underlying psychologic problem as well. In these persons, a vacation at the seashore or in the mountains usually results in rapid improvement. Adequate sedation is helpful, but care should be taken that the patient does not excoriate the skin during a disturbed, half drugged sleep In selected cases of nonchronic dermatitis, cortisone therapy is of decided benefit.

The psychosomatic causation of alopecia areata has not been definitely established, although a psychosomatic origin seems probable in view of the studies of Kaplan and Reisch, and me. These studies emphasize the importance of recent psychic trauma in nearly every patient studied. In addition, there *is* a *definite* background of insecurity feelings of inferiority and disappointments regarding advancement in life. The ordinarily self-limited nature of the disorder makes these patients good candidates for a reassuring and local stimulating type of therapy

A somewhat similar situation obtains in rosacea, but here over responsibilities and social anxieties are more prominent features. Symptomatic treatment usually results in temporary arrests, but relapses are frequent. Such relapses are due commonly to the unavoidable continuation of the unfavorable life situation and to the pronounced tendency of the patients to flush at the slightest provocation.

Psychogenic urticaria is usually of a temporary nature and gen-

erally stems from frustrating situations engendering hostility and resentment. A symptomatic regimen with the antihistamines plus or minus cortisone and some discussion with the patient regarding the nature of the illness usually suffice.

Symmetrical erythema complicating emotional hyperhidrosis is often difficult to control. I reported its occurrence in soldiers during pre or postcombat situations, and Klauder mentioned its development following the use of erythema-producing chemicals in industry. I have not found x-ray therapy of much value and have had to resort occasionally to sympathectomies. The dominant and seemingly ingrained anxiety usually exhibited by these patients makes them poor candidates for psychotherapy.

Regarding acne vulgaris and psoriasis, these diseases are never primarily psychosomatic in my opinion.

A few years ago I summarized my findings in vesicular neurodermatitis of the hands. This entity may occur as a reaction to a dominant anxiety and may develop without antecedent disease or as a reactivation of a previous dermatophytid. Ordinarily symptomatic therapy and reassurance are all that are needed, although relapses are common.

The influence of psychologic factors as potentiating agents in the development of sensitization dermatoses is probably due to the liberation of acetylcholine at nerve endings, in combination with other influences leading to vasodilatation. The macerating effects of hyperhidrosis may increase the ease of absorption of allergens.

In closing, mention should be made of the potentiating effect of nervous stress on the development of herpes simplex and the equally puzzling effects of suggestion in the cure of verruca vulgaris. Allington among others has discussed the treatment of warts by psychotherapy. Occasionally a dramatic result may be obtained in patients with severe and disabling plantar warts. Obermayer and Greenson reported such a case, and an equally impressive cure was observed in a patient of mine who was treated by posthypnotic suggestion.

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5

Eczematous Dermatitis

By
V Pardo-Castello

DERMATITIS is any kind of cutaneous inflammation. Eczematous dermatitis, on the other hand, is a peculiar type of cutaneous inflammation characterized by redness and vesicle formation, occurring in ill-defined patches of varying size and shape. Itching is always present. The lesions start as red spots and rapidly become vesicular with the subsequent formation of crusts and scales. The process ends with the establishment of normal skin.

Eczematous dermatitis is also called eczema, dermatitis venenata, infectious eczematoid dermatitis, contact dermatitis, allergic dermatitis, atopic dermatitis or eczema, seborrheic eczema, and a variety of other names. I believe that all of these terms should be discarded in favor of the simpler and more comprehensive name, eczematous dermatitis, which means dermatitis occurring with one or more episodes of redness and vesicle formation.

I also believe that the unhappy term, atopic dermatitis, should be applied exclusively to the disorder known as neurodermatitis, which may in turn become eczematized as a result of scratching, the application of irritating drugs or other chemicals, or in occasional instances, from endogenous toxins acting in association with the external factor

Eczematous dermatitis is the most common skin disease. It represents the usual response of the skin to injury whether acting on the skin from the outside or from the inside. Any number of substances may cause this disorder on coming in contact with the skin, either as a primary irritant or as allergens. Micro-organisms are also important offenders acting from the outside. Foods

drugs, and emotional stresses constitute the chief precipitating factors from the inside.

Histopathologically eczematous dermatitis is characterized by a succession of inflammatory changes. The dilatation of blood and lymphatic vessels seen in early stages of the disorder and which is expressed clinically by redness of the skin, is soon followed by both intracellular and intercellular edema, vesicles and occasional bullae. The perivascular infiltrate, which at first is composed mainly of lymphocytes and a few neutrophils, rapidly becomes dense, with a predominance of lymphocytes, neutrophils, and histiocytes. Varying numbers of these cells may migrate through the epidermis. The frequent occurrence of pustules and crusts is caused by infection with pyogenic organisms.

In more advanced lesions the entire horny layer may be lost, leaving the skin dripping wet with serum which, when it dries on clothes and dressings, makes them appear starched. Involution may be spontaneous, or it may result from treatment. Redness, vesicles, and oozing gradually subside, and a normal skin is formed, which remains covered with scales for quite a while. In some patients, signs of inflammation may persist for a long time, due to the fact that the normal acid mantle of the skin is not restored. The resistance of the skin to both exogenous and endogenous irritants may be lowered indefinitely This is particularly so in the case of allergens acting from the outside.

The etiologic agents of eczematous dermatitis are many and varied. I believe that they may be classified easily and understandably as follows

Contacts	Primary irritants, hypersensitivity and allergy
	Allergy (mainly due to drugs)
	Metabolic disturbances (diabetes, hormonal and hepatic disturbances, etc.)
	Toxins and infections (focal infections)
Internal factors	Inhalants (wool, dust, fungi, smoke, etc.)
	Peripheral vascular disease (capillaritis, stasis, varicose veins, etc.)
Infections	Pyogenic bacteria, fungi, Ps. aeruginosa, etc.

Psychosomatic factors Emotional stress inducing itching, scratching, loss of sleep, etc.

Unknown factors

The cause cannot always be determined, due to lack of cooperation on the part of the patient, multiplicity of causative factors, or because the original factor has been removed. The line of demarcation between *etiologic agents is sometimes hazy* especially when several of them act successively or at the same time. Then again, the episode may subside before the cause has definitely been established, or the patient may have been given so much treatment for a large number of hypothetical disorders that it is impossible to obtain a clear-cut history of the factors surrounding the onset of the present disorder

Contact eczematous dermatitis is caused by contact with an irritating substance. It constitutes about 80 per cent of all cases of eczematous dermatitis. Persons with a dry light-colored skin are more susceptible than those with greasy dark skins. Children, especially babies, are more often affected than adults. Persons leading a sedentary life are more subject to the disorder that those used to an outdoor life. Soap and other detergents deprive the skin of its natural defenses, resulting in decrease of hydrogen ion concentration. This creates a favorable environment for the development of eczematous dermatitis. In infants, soap and talcum powder frequently act as causative agents, the sensitization thus established sometimes persisting throughout life. The multiplicity of possible causative factors often greatly taxes the mental and investigative powers of the attending physician.

Primary irritants are substances which act directly on the skin without the intervention of the allergic mechanism. Practically any chemical may act as a primary irritant, either as such, or combined with other chemicals in such commercial products as battery fluid, explosives, cleaning and polishing fluids, varnish, detergents, fertilizers, and others. These substances together with almost any drug, cause primary irritant eczematous dermatitis in many persons coming in contact with them for the first time. The removal of the offending agent, together with proper treatment of the condition, usually effects a speedy cure. Patients may ac-

quire increased tolerance through repeated contacts, which is exactly the opposite of what happens to those with allergic dermatitis.

Allergic contact eczematous dermatitis frequently results from contact of the skin with a substance acting as an allergen. Repeated contacts over a period of days, weeks, or months, are usually required for the development of sensitization. The reaction occasionally takes place after the first contact, in which case it is an expression of hypersensitivity acquired congenitally or through previous contacts with the exciting allergen. Hypersensitivity of this kind induces inflammatory reaction of the skin on coming in contact with insecticides, plants, and flowers

Among the offending plants and flowers are Rhus toxicodendrum, Rhus diversiloba, Commocladia dentata, Metopium browneii, Hura crepitans, Euphorbia lactea, and Hippomane mancinella, all of which are commonly found in tropical and subtropical America. Plants often induce a particularly vicious reaction, marked by the sudden appearance of vesicles and bullae on an intensely inflamed skin. The essence of bergamot, which is present in pure form in the rind of the lime and the bergamot orange and as a component of toilet water and perfume, occasionally causes breloque dermatitis upon exposure of the skin to sunlight. Persons lying in the sun on grass containing essential oils sometimes develop similar lesions.

Cosmetics are the greatest source of contact dermatitis in women, often inducing areas of redness with a few vesicles which persist for a long time. The use of lipstick frequently causes acute or chronic cheilitis with intense redness, oozing, and scaling, showing a tendency to spread from the lips to the nose and chin.

Insecticides, especially those containing pyrethrum, are a common source of allergic contact dermatitis.

The use of nail polish often causes redness and scaling of the eyelids, back and sides of the neck, and chest. Although nail polish rarely involves the back of the fingers, it occasionally causes eczematous dermatitis of the nail bed, with subsequent loosening and shedding of the nails.

Mascara and other pigments to shade the eyelids and eyebrows are common causes of eczematous dermatitis of the lids and con-

junctivae. Men occasionally develop dermatitis due to contact with women wearing cosmetics.

Allergic eczematous dermatitis is not infrequently caused by contact of the skin with iodoform, the sulfonamides, phenol, boric acid, tincture of arnica, chloroform, mercurial salts, chrysarobin, sulfur picrates, and penicillin. The area of involvement may be extensive or small and limited to the site of contact. Patients with generalized involvement of the skin are usually acutely ill. Occasionally the condition ends fatally

A partial list of other causes of this type of dermatitis includes varnishes, enamels paints, furniture stain and polish, aniline dyes in clothes upholstery leather curtains, and other dyed materials; nickel in watches, jewelry keys, coins, and door handles nylon, rayon, synthetic fibers steering wheels, seat covers phosphorus in matches and match boxes.

The feet are commonly the site of eczematous dermatitis. The most frequent exciting agents are synthetic rubber cements, and dyes used in the manufacture of shoes. Involvement of the heel and instep is common in women wearing high heeled shoes which are usually too small for them. Nylon stockings and undergarments are frequent offending allergens Dermatitis due to these contacts often spreads over large areas of the skin, making it sometimes difficult to discover the original site of the disorder

Toilet seat dermatitis occurs commonly in children on the buttocks and back of the thighs, and is due to contact with paints, enamels, or wood stains applied to toilet seats.

Babies are particularly apt to develop eczematous dermatitis from contact with such substances as wool and antiseptic oil which act as allergens on skin which has lost its protective acid mantle from a previous irritation due to the use of too much soap Search for possible allergenic substances should include the perfumes, cosmetics and clothes worn by the mother or nurse. Even their dandruff can make trouble. Rough fabrics in diapers and waterproof protectors should not be overlooked. Scratching often leads to infection.

Occupational dermatitis is simply eczematous dermatitis occurring in industrial, agricultural, and professional workers from contact with substances handled in their work. The use of sol-

vents, soaps, and detergents, together with injury caused by rubbing and scratching, frequently aggravates the dermatitis.

Eczematous dermatitis due to contacts may be superimposed on neurodermatitis, resulting usually from scratching or from the application of an irritating ointment or lotion. A vicious cycle of itching, scratching, nervousness, and loss of sleep is easily established and kept up seemingly *forever* Many cases of so-called atopic dermatitis fall into this category

The detection of the causative factor in contact eczematous dermatitis is begun by taking a careful history of the patient's contacts in his home and place of employment. A physical examination is then made.

Patch tests should not be employed until a suspected contact has been fairly well established by the history and by observation of the patient. The patch test is made with the suspected material placed in contact with normal skin, the form and concentration in which the materials are applied depends on whether it is a solid or a liquid. Complete lists of allergens and the technique of patch testing may be found in texts on allergy

ECZEMATOUS DERMATITIS DUE TO INTERNAL CAUSES

Drugs, especially the sulfonamides and penicillin, are the main exciting allergens in this type of eczematous dermatitis. The allergic person often responds to the ingestion or parenteral use of these drugs, with an eruption consisting of erythema, vesicles, and bullae. The suppression of the drug, together with the use of local and systemic therapy usually brings on a rapid recovery However reactions caused by arsenic or gold may persist for a long time, due to deposit of insoluble metallic salts in the skin. The eruptions caused by these metals are widespread, often involving the entire skin. In these cases, the hair and nails are often shed. In some patients, the lesions are limited to the skin folds, face and neck; in others, vesicles are present in profusion, and both oozing and edema are prominent. The prompt use of intramuscular injections of 2,3-di mercapto-propanol (Bal) hastens involution of the eruption by liberating the metal from the tissues, from which it finds its way to the kidneys, where it is excreted as a soluble salt.

Dermatophytosis of the feet is not infrequently complicated by infection with pyogenic organisms. Eczematous dermatitis produced in this manner is associated with sensations of burning, itching, and pain.

PSYCHOSOMATIC ECZEMATOUS DERMATITIS

Itching is a common expression of emotional stress. It is a safety valve for pent up emotions and for the mental stress caused by life s unpleasant situations. The psychic implications of itching are discussed elsewhere.

Scratching results in excoriations, bleeding, and lichenification, the persistence of which irritates the skin still more, inducing eczematous dermatitis. Many patients with so-called atopic dermatitis belong in this category Lesions of this type, occurring about the genitalia of persons suffering from suppressed sexual desire, are particularly common in sexual perverts Others scratch and irritate any part of the skin that their disturbed minds may dictate.

The character of modern city life replete with frustrations, unsatisfied desires, financial worries, spiritual shocks, noise, and other psychic thorns, serves to explain the psychosomatic background of many patients with eczematous dermatitis.

UNKNOWN CAUSES OF ECZEMATOUS DERMATITIS

It is sometimes impossible to determine the etiologic factor in patients with eczematous dermatitis. Repeated episodes of the disorder may occur in rapid succession, in spite of excellent medical care These relapses can often be attributed to lack of cooperation on the part of the patient in neglecting to tell the physician how he broke his diet, used soap or rubbed in an ointment which his son had used for ringworm Of course, some patients are ignorant, while others are just plain stupid. There is very little that we can do for such persons, but we must not forget to be charitable, as our failure to discover the cause of their troubles is really not their fault.

A histologic examination may be required to differentiate eczematous dermatitis from dermatitis herpetiformis prurigo, neurodermatitis without superimposed dermatitis, exfoliative

dermatitis, pellagra, mycosis fungoides, and seborrheic dermatitis. However even after prolonged study of the histologic sections, the diagnosis may remain in doubt.

TREATMENT

Patients with acute eczematous dermatitis should be treated with as much solicitude as possible. Bathing in water containing starch or oatmeal (Aveeno) reduces the inflammation and congestion of the skin and also soothes the nerves. Patients are always grateful for the relief afforded by baths of this type.

Wet dressings of aluminum acetate or boric acid are particularly effective in acute eczematous dermatitis of the legs, face, external genitalia, and under the breast. Their application for three or four days usually stops the oozing Constant care to avoid chilling the patient is required, as the dressing must be kept wet. A loose and barely moist dressing is worse than nothing.

The application of phenolated calamine liniment N.F several times a day between baths or wet dressings adds considerably to their effectiveness.

After the oozing and crusting have subsided, which is generally a matter of three or four days, the following ointment may be applied several times a day with a wooden tongue depressor:

R Phenol	1.0
[illegible]	15.0
[illegible]	15.0
[illegible]	25.0
[illegible]	100.0

Many patients get well with this treatment alone, but the use of a laxative and a diet of milk, rice, potatoes, fresh or stewed fruits, and dry toast help considerably in bringing about a more rapid cure. In nervous patients, the use of bromides or barbiturates in small doses, together with bed rest, promotes recovery

No soap or soap substitute should be used. Patients should bathe and wash as little as possible, using only colloidal suspensions of starch or oatmeal for cleansing purposes. Only cotton or linen clothing should be worn.

The topical application of a 10 per cent ichthyol or tar paste is very effective in patients with subacute eczematous dermatitis. Lassar's paste, with 10 per cent ichthyol added, is useful in patients with either the subacute or chronic form of the disorder. White's classic coal tar ointment is particularly serviceable in eczematous dermatitis occurring in infants. The prescription for this follows

R	Crude coal tar	1.0
	Zinc oxide	6.0
	Corn starch	12.0
	Petrolatum	80.0

The ointment should be applied several times a day without removal of previous applications.

Patients with chronic eczematous dermatitis usually respond favorably to the use of an ointment of salicylic acid or a paste of oil of cade, resorcin, or crude coal tar in concentrations from 3 to 10 per cent, depending on the amount of thickening and scaling of the skin. Olive, cotton seed, or mineral oil may be used for cleansing.

The use of wide-spectrum antibiotic ointments in infectious eczematous dermatitis is world wide. I still like to prescribe 3 to 5 per cent ointment of ammoniated mercury provided the disorder is not widespread, when the possibility of excessive mercury absorption must be considered.

The use of alcohol, coffee and other stimulants should be denied to many of these patients, particularly those having generalized eczematous dermatitis of unexplained origin. The employment of a soft diet, the elimination of foci of infection, and keeping the bowels open are highly indicated.

Daily intravenous injections of a 10 per cent solution of sodium bromide, in combination with small doses of the barbiturate by mouth, are helpful in quieting high-strung patients. My results with the antihistaminic drugs have not been impressive. The use of cortisone in doses of 100 mg. daily is indicated in patients with extensive involvement of the skin.

Needless to say the detection of the causative factor should lead to its removal from the patient's environment or if this is impossible, enable the patient to avoid contact with it. A thorough physical examination should be made, and a history of former illnesses taken. Full use of the laboratory is made in all patients under my care, especially those in whom the cause is undetermined.

A few x-ray treatments of 75 r each at weekly intervals are useful during the chronic stages of the disorder and after the acute manifestations of earlier stages have subsided. More than five or six such treatments should not be given. The use of ultraviolet radiation is indicated in patients showing erythema and scaling, treatments being given twice weekly

The use of Urbach's Propeptones and antiallergic preparations containing polythiosulfates is thoroughly discredited. Calcium gluconate in the form of intramuscular or intravenous injection frequently proves effective in the early phases of eczematous dermatitis.

The management of patients with psychosomatic eczematous dermatitis is difficult. Lesions caused by scratching are best treated by the application of an occlusive dressing which should be left in place for five or six days. The application of an antipruritic remedy under the bandage is advisable. Hydrocortisone ointment (1 per cent) is very effective in controlling severe itching A frequent difficulty encountered in treating these patients is that they often transfer their scratching habits to some other area of the skin, which results in the formation of another patch of eczematous dermatitis. Insomnia and indigestion contribute to psychic unbalance, helping to set up a vicious cycle of scratching and dermatitis which not infrequently makes an incurable invalid of the patient.

A man does not have to be especially schooled in psychiatry to help these unfortunate persons A sympathetic attitude, together with personal interviews, helpful advice, and a liberal sprinkling of common sense, goes a long way in getting them out of their mental traps. One thing is certain: the busy specialist, seeing from 80 to 100 patients a day has no business caring for these hapless persons.

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6

Neurodermatitis

CIRCUMSCRIBED DISSEMINATED, AND ACUTE EXUDATIVE

By
Harry L. Arnold, Jr

NEURODERMATITIS means many things to many men. It implies, in general, a pruritic dermatitis caused by nonorganic dysfunction of the central nervous system. Among North American dermatologists, the word is generally applied to three cutaneous neuroses circumscribed neurodermatitis, disseminated neurodermatitis, and acute exudative neurodermatitis. It is under these designations that we will consider its causes, its diagnosis, and its management.

Circumscribed neurodermatitis still goes by a variety of names. Obsolete are the old designations prurigo ferox, prurigo pudendalis, *lichen agrius, eczema papulorum, and others. Still in use,* chiefly by those who do not believe the disease is psychogenic, are lichen simplex, lichen simplex chronicus, and lichen Vidal. By no means obsolete are the symptom names pruritus ani, pruritus scroti, pruritus vulvae, otitis externa, and others which include occasional examples of diseases other than circumscribed neurodermatitis.

Disseminated neurodermatitis is often used as a synonym for atopic (flexural, allergic, nutritional or infantile) eczema or atopic dermatitis some use it also to mean widespread lesions of circumscribed neurodermatitis, most regard the two meanings as essentially synonymous.

Acute exudative neurodermatitis is an acute severe, usually localized, and weepy erythema, sudden in onset, often as sudden

in subsidence, perhaps most often diagnosed by exclusion of the first-suspected physical or chemical causes.

A tabular summary of the salient features of these three disorders may clarify the similarities and differences among them.

NEURODERMATITIS

Clinical Features	*Circumscribed*	*Disseminated*	*Acute Exudative*
Usual age of onset	Adult life	Infancy	Adult lif
Basic skin lesion	Lichenification	Lichenification	Weepy erythema
Mode of onset	Sudden itching, slow thickening	Sudden itching, slow thickening	Sudden burning and itching, sudden redness and weeping
Atopic background	Usually none	Almost always	Usually none
Symmetry of lesions	Unusual	The rule	Unusual
Remissions	Occasional	Exceptional	Frequent
Commonest sites of involvement	Neck, genitalia, eyelids, flexures	Flexures and face	Around eyes and mouth often
Intolerance to bland medicaments	Seldom	Seldom	Very frequently
Aggravation by foods	Infrequently	Occasionally	Rarely if ever

CIRCUMSCRIBED NEURODERMATITIS

Clinical features. The essential diagnostic features of this disease, call it by what name you will, are two more or less sharply circumscribed lichenification of the skin, and paroxysms of irresistibly pleasurable pruritus relieved only by pain, which is usually produced by rubbing or scratching to the point of soreness. Sometimes very hot water is used. The result is the same complete cessation of itching until the next paroxysm occurs minutes or hours later

In 500 consecutive cases of circumscribed neurodermatitis seen in my practice, there were 283 females and 217 males. The duration of the disease ranged from a week to 40 years the average being 23 7 months. Patients ranged in age from two to 73 years, with an average of 24 years. A solitary lesion was presented in 350 cases and multiple sites were involved in 150

The racial distribution of cases showed rather striking disparity taking the incidence in Caucasian patients as 1, the disease occurred with three times this frequency in both Japanese and

Chinese and with seven times this frequency in Filipino patients. This is partly attributable to the fact that most Filipino patients with readily manageable disorders receive their medical care on the sugar plantation where they work; those who come to my office present for the most part disorders that are difficult to cure. So many Japanese and Chinese patients attend our group regularly however that the higher incidence of neurodermatitis in these groups probably reflects greater liability to it.

As to sites of election, the neck was the commonest single location, being involved altogether in 117 out of 500 cases.

The genital region was the next commonest in my series; the scrotum was involved in 59 cases, and the vulva in 31 a total of 90 with genital lesions.

A highly characteristic site is the mammary areola on one side. Aside from a severe seborrheic dermatitis and Paget s disease of the breast, there is no important disorder with which neurodermatitis of this area is likely to be confused.

The eyelids are also highly characteristic as a site for this disease; 23 cases, all with involvement of either both upper lids or more than one area, were observed in this series.

In the great majority of cases, itching occurs almost exclusively during periods of leisure on arriving home from work, on finishing the dinner dishes· on completing a bath (or sometimes during it) on undressing for bed, on actually going to bed, or after falling asleep. Shaffer and Beerman have made this same observation. Itching is also elicited in many cases by perspiration, probably a mechanical effect due to keratinous plugging of sweat pores, which produces a sort of localized miliaria and triggers the paroxysmal itching at times

The itching is usually sudden in onset and almost always maximal. Patients rarely report the occurrence of mild itching Relief of itching by a few rubs, such as might be administered to a mosquito bite, a patch of ringworm, or an itching scalp is seldom experienced. Once the patient yields to the urge to scratch, there is no stopping until scratching becomes painful, and this seldom happens until the skin has been injured enough to elicit bleeding or at least some serous oozing Nearly every patient will admit that "it feels so good you just can t stop," and many will

acknowledge with some embarrassment that the pleasure is exquisitely intense. I have heard more than one patient compare it favorably with that of coitus.

All of these diagnostic features are equally true of disseminated neurodermatitis or chronic atopic dermatitis. The only basis for distinguishing between them is the tendency of the disseminated variety to grow out of infantile atopic dermatitis (and therefore to occur in "atopic individuals") and to be symmetrical, often involving the face, neck, and knee and elbow bends. Obermayer Kierland and Walsh, Cormia and many others believe, as I do, that there is no fundamental difference between the two as to pathogenesis, etiology or treatment. Many men, however still separate them.

Mimicry of psoriasis is fairly common in solitary lesions of circumscribed neurodermatitis and still more common when multiple lesions are seen. The resemblance may be so close, both clinically and histologically that the differentiation depends on definitions e.g., may psoriatic plaques itch in paroxysms of irresistible severity? May an intensely itchy psoriatic plaque remain as the solitary manifestation of the disease over a period of many years? May multiple lesions of circumscribed neurodermatitis be associated with psoriatic pitting of the nails? May psoriatic plaques present eosinophiles in the cellular infiltrate? I am sure that I have seen cases in which an initially classic, circumscribed neurodermatitis underwent transition into psoriasis as well as cases in which the reverse transition occurred. I am not at all certain that they are basically different diseases, if by different is meant "having different causes, a different outlook, and different responses to treatment."

Mimicry of lichen planus particularly hypertrophic lichen planus of the skin, may also be a diagnostic stumbling block, and here too the question arises as to definitions of the two entities. Histologic differentiation is usually possible, however in this situation.

Pathogenesis. As to the cause of circumscribed neurodermatitis, there is widespread acceptance of the view that the disease is associated with "nervous irritability "anxiety" and so on. My experiences have led me to the same conclusion reached by

Obermayer Doyle, Allerhand and his associates, Levy Seitz, and others, that the fundamental cause *is* suppressed hostility occurring in a naturally aggressive person with only limited ability to express aggression outwardly

The typical patient with circumscribed neurodermatitis is a pleasant individual, eager to be liked and concerned for the good opinion of others. He or she has conceived (often enough for good reason) a feeling of serious resentment or actual hostility toward some person against whom this emotion can not be openly displayed. Indeed, the patient finds it painful, in many instances, even to *think* about his angry feeling toward this person.

This feeling is therefore repressed into the subconscious mind and with it the sense of guilt it has engendered in its own right. Here it no longer makes the patient feel unhappy· indeed, it is not at all unusual for these patients to display an almost preternatural serenity—*la belle indifférence* of the French neurologists. The superficial inquiry "Are you nervous?" or "Are you unhappy?" will often elicit a confident denial, the accusation "You have a suppressed emotional conflict" may elicit, as it did from one of my patients (Case 1, below) in whom a serious conflict was later discovered, the remark "Why that s just ridiculous!"

Even in the subconscious, however these feelings of hostility and guilt create an unmet emotional need the need to hurt the object of the hostility and to punish the object of the guilt. This need periodically reaches the level of consciousness, and when it does the patient gratifies it by a physical attack on his own skin.

This explanation helps to account for two curious features of the pruritic attacks the fact that only pain will relieve them and the fact that they are almost always preceded by a sense of tension and followed by a sense of extreme relaxation or even lassitude. It helps to account, too for the timing of the attacks, since presumably the conscious mind is most accessible to the contents of the subconscious mind when it is least occupied, that is, during periods of leisure and during sleep.

Psychiatric management. The psychiatric approach *is no more* regularly successful in the management of circumscribed neurodermatitis than it is in the management of diseases more generally accepted as being of psychogenic origin. Moreover there are

spontaneous remissions of the disease at times, though most cases which have lasted as long as six months or a year are likely to continue for several years at least. Furthermore, cures are occasionally achieved either with ordinary dermatologic measures, destructive treatments or x ray therapy

Notwithstanding these objections, the dramatic cures occasionally achieved through the discovery and "ventilation of a suppressed emotional conflict or through the removal of its cause constitute impressive if inferential evidence of the essential correctness of the psychosomatic view of the disease. The selection of cases for this type of treatment is difficult, and there are few guides to help the beginner Some capacity for emotional insight is necessary in the patient as well as in the doctor It may be helpful, too to have first exhausted the patient s confidence in a more direct dermatologic approach.

For the actual conduct of psychotherapy Obermayer has outlined a practical and sound program help the patient to achieve emotional catharsis, to express physically (in words, by weeping, etc.) the suppressed emotion, if it can be uncovered encourage dependence and reliance on the physician, accept the disease realistically for what it is, an emotional safety valve, and stop searching frantically for the magic cure. If these things cannot be done or fail to help psychiatric referral is warranted for certain cases.

I have found it practical to begin by explaining the psychosomatic mechanism to most patients who have the capacity to understand it. Simple, intelligible language is used, and further clarification is achieved through the use of examples. Some patients are merely told that they are hurting themselves for the relief of nervous tension just as a little boy angry at his parents but too fearful of the consequences to attack them physically may kick a boulder or a bedpost to relieve his feelings. Some patients are told of actual cases in which the suppressed and concealed reason for the causative conflict was discovered.

A few patients will voluntarily proceed from this beginning into a frank exposition of their problems, occasionally with real perception of the basic conflict, though often this is disguised so as to make it less painful for them. Many more patients will

agree that this explanation fits their case to a T but will either refuse to discuss the basic conflict or else deny sometimes with perfectly convincing sincerity any knowledge of such. A few *patients will simply reject the entire suggestion as implausible if* not downright fantastic. Many of these negative responses turn out to have no basis in fact. causative conflicts are often ultimately discovered in patients giving this response.

Some illustrative case reports follow (Cases 1, 2, and 3 have previously been published)

Case 1. An attractive, intelligent Chinese schoolteacher in her early twenties complained of a paroxysmally itchy lichenified 3 by 5 cm. plaque on one leg of some 12 years duration. Told that she had it because of emotional conflict which she had suppressed because she could not bear to think about it, she laughed merrily and informed me that the suggestion was ridiculous. I told her that I was not surprised that she felt that way and that it did not change my belief about the cause of her trouble. Tar paste was prescribed, and she left.

Three weeks later she telephoned me to ask if I would be interested in knowing that she had learned the reason for her skin lesion. I said of course I would be, and she told me that her sister had, on learning what I had said, told her that she knew the cause of the lesion. It was, she said, where their father had struck her with a stick at the age of 11, to punish her it had broken the skin, and the injury had never really healed.

And you know doctor she continued, ever since she told that, it hasn't itched once, not once! And what's more, I feel like a new person, so relaxed and self-confident! I never felt like this before. It's wonderful!"

Two weeks later she was in the hospital, receiving shock therapy for acute paranoid schizophrenia, manifested primarily by hallucinations and delusions. She made a good recovery and the leg lesion never itched again, though the lichenification was very *slow to subside.*

Comment. This case illustrates three often-observed facts that an extremely serious emotional conflict (in this case, deep-rooted hatred of the father) may be so thoroughly suppressed that the patient is completely unaware of it, that "habit," so often blamed for the recurrent episodes of scratching, is not necessarily a factor

and that abrupt introduction of a serious conflict at the conscious level of thought may precipitate a psychosis.

Dermatologic management. Purely dermatologic treatment is virtually impossible to achieve Adventitious psychotherapy as Twiston Davies has aptly labelled it, is a part of all medical treatment. The physician s reputation and prestige, his professional sympathy and the dependence of the patient upon him, all play a part in relieving the patient s underlying tension.

There are a good many cases, however in which active psychotherapy is not feasible, and the adventitious kind is not adequate. Language difficulty may interfere with it, so may a low IQ in some patients one arouses active hostility by this approach, sometimes even a searching inquiry will reveal no basis for conflicts and of course not all physicians are emotionally qualified to undertake this sort of therapy It is desirable in most cases and necessary in many to treat the lesion or lesions dermatologically

There is no "best" method of doing this Treatment must be adapted to the individual case. Dermatologic treatment may be divided, however into three general types: soothing and reducing, systemic; and destructive.

Of the soothing and reducing medicaments, hydrocortisone in 1 or 2 per cent concentration in an ointment base is undoubtedly the most effective. It is rarely necessary (and still more rarely helpful) to change from this to either an antihistaminic ointment, a local anesthetic ointment, or a tar preparation.

Among the antihistaminics for topical use, there is little to choose· none is uniformly effective, and all may sensitize the skin The same may be said of local anesthetics

Of tars, the most uniformly effective is crude coal tar the most acceptable forms of which are Zetar brand of tar (which can be washed out of bedding and clothing) and Squibb s Tar quinor ointment (which does not stain skin or clothing, and contains quinolor to minimize tar pyoderma) Zetar may be employed pure or in baths ointments, pastes or varnishes (in 5 to 10 per cent solution in chloroform) Another useful form of coal tar is Liquor picis carbonis N.F., which may be used undiluted or in lotions or liniments in any strength desired. Colorado shale oil, not yet commercially available, has been highly recommended

for external use. Belisario reports excellent results in nuchal plaques from painting the lesions weekly with podophyllin in compound tincture of benzoin, starting with 5 per cent and working gradually up to 20 per cent strength.

Systemic treatment may be considered under three general headings sedation (for which phenobarbital, 15 mg three times daily is hard to improve upon) "relaxation (with chlorpromazine, 10 or 25 mg. three times a day or Rauwolfia alkaloids) and the specific hormonal antidote hydrocortisone or cortisone orally in sufficient dose to control the symptoms. The first of these, phenobarbital, is frequently very helpful indeed. The second, chlorpromazine and the Rauwolfia drugs, is too new to have been adequately evaluated as yet, I have found it somewhat disappointing The third is rarely justifiable in circumscribed neurodermatitis.

Destructive treatment is ordinarily reserved for the most thickened plaques of neurodermatitis of small size (seldom over 5 by 8 cm.) and of long duration (a year or two at least) in patients who are not suitable for psychotherapy The mildest form, which is really suppressive or sedative rather than destructive, is superficial x-ray therapy Low voltage from 60 to 100 KV and little or no filtration should be employed, with weekly doses of 80 to 100 r for not over ten weeks except in very elderly patients The casual exhaustion of a patient's tolerance for irradiation, merely to achieve a few weeks relief of itching in a plaque of neurodermatitis, cannot be too strongly condemned. Exceeding his tolerance and producing a permanent radiation burn is of course even worse and it can result from a few doses of x-rays here and a few there, given by a series of well-meaning physicians, each unaware of what his predecessor has done. X ray therapy should never be used as the chief means of treatment. It should be used reluctantly and conservatively and primarily as an adjunct to other methods. It rarely accomplishes a lasting cure, and it is loaded with potentialities for serious harm.

Actually destructive treatment of thickened, lichenified plaques may be surprisingly effective and is far safer paradoxically than irradiation. The more conservative method is to scrub the lesion vigorously with a rough stiff applicator (a gauze-wrapped wooden

tongue-depressor is convenient) wet with 20 per cent sodium or potassium hydroxide solution, until it is eroded deeply enough to be painful. The lye is then sopped off with boric acid solution or vinegar the lesion dried by blotting, and a boric acid ointment dressing applied. The moderate pain produced in this way seems *to be accepted by the patient as a substitute for the pruritus,* and complete relief of itching is often accomplished by a single scrubbing Care should be taken not to remove the epidermis completely in an area more than a few millimeters wide, especially on the ankle (where healing will be slow) or in a conspicuous area (where an unsightly scar might result)

Another destructive method of treatment is to anesthetize the itchy area in a quasipermanent fashion by multiple superficial subcutaneous injections of 60 to 95 per cent ethyl alcohol containing 2 per cent procaine hydrochloride. Usually 0.1 cc. aliquots are injected at 1 cm. intervals over the whole itchy area. The pain is fairly severe but patients tolerate it very well, and the relief achieved is often remarkably complete and long lasting

Two case reports will illustrate potential drawbacks of this method, each of them representative of many similar cases.

Case 2. A middle-aged Filipino laborer with a leathery paroxysmally itchy plaque on one shin, had been treated intermittently in the St. Francis Hospital out patient department for a duodenal ulcer which had been asymptomatic since the appearance of the skin lesion three years before. After some weeks of *topical therapy had given no relief* the entire plaque, which measured about 4 × 8 cm., was injected at intervals of 1 cm. with 0.1 cc. aliquots of a 2 per cent solution of procaine hydrochloride in 95 per cent ethyl alcohol. Itching was completely relieved, but he returned a week later complaining of typical ulcer pain which had begun four days after the plaque was anesthetized.

Comment The cessation of ulcer pain when the skin lesion began and its return when the emotional release of self injury by scratching was shut off by the alcohol injections, certainly invite the supposition that the two mechanisms were, for this man, alternative ways to relieve pent-up nervous tension. It is not so curious that this should happen occasionally as that it should happen so infrequently

Case 8. An attractive Filipino housewife in her late twenties complained of an unbearably itchy lichenified plaque across the dorsum of the right foot of about a year's duration. She steadfastly denied any emotional conflicts or troubles of any kind. The plaque was vigorously scrubbed, to the point of soreness, with 20 per cent sodium hydroxide solution on a gauze-wrapped tongue-depressor. Boric acid ointment was dispensed for daily application.

She was next seen almost three years later. The treated plaque had promptly healed and had never recurred, but she had developed a new plaque on the same foot and three on the other foot.

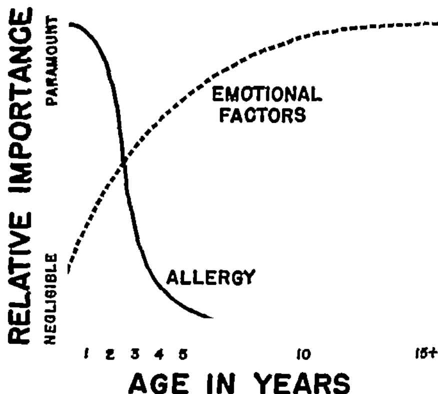
At this visit she reluctantly and tearfully disclosed the sad story that she had been involved in a love affair with her husband's closest friend for almost four years and was unwilling to hurt her husband's feelings by telling him of it or even by asking him for a divorce. No solution of this impasse was arrived at, and she was not seen again.

Comment This case illustrates a fairly common occurrence driving the disease from one site to another (or several others) by overly vigorous therapy The process seems analogous to creating leaks in a steam boiler by hanging extra weights on the safety valve.

DISSEMINATED NEURODERMATITIS

Clinical aspects. The term disseminated neurodermatitis is generally used as a synonym for chronic atopic dermatitis. The individual lesion differs in no essential respect from that of circumscribed neurodermatitis: a lichenified, paroxysmally itchy plaque. The minimum diagnostic criterion for applying the adjective "disseminated" is not, as one might suppose, a wide-spread distribution, though symmetric involvement of face, neck, elbow and knee flexures, sometimes ankle and wrist flexures or even entire integument, is the rule. The essential feature is that the disease has its onset in infancy childhood, or adolescence, and persists into adult life. If this is true and involvement is facial or flexural or both, symmetry is not essential to the diagnosis.

The relationship between the allergenic atopic dermatitis of infancy and the psychogenic disseminated neurodermatitis of adolescence or adult life can be represented by plotting the rela-



tive importance of allergic factors and of psychic factors on the ordinate and the patient's age on the abscissa (Fig 1)

After the age of 2 or 3 years, allergy plays a minor role, and the disease continues on a primarily psychogenic basis. This conclusion is suggested by the fact that these patients are rarely able to help themselves even slightly by avoidance of foods or inhalants or by submitting to desensitization by the fact that Williams, in Vancouver was able to clear a series of cases of this disease much earlier than a series of dermatologically treated controls, just by persuading their mothers to accept them and behave affectionately toward them by the fact that psychometric testing has regularly revealed the pattern of suppressed hostility suppressed resentment, a strict and punitive super-ego, hostile-dependent attitudes toward the mother and so on. Many pa-

tients become aware through self observation that their skin is an emotional barometer

Management. The outlook in disseminated neurodermatitis for cure or even relief by ordinary psychiatric or dermatologic measures is not good. The allergic approach may occasionally offer patients a little relief from acute exacerbations a psychiatric approach may help them to tolerate their disease a little better and medication, external and internal, may make life a little easier for them. I have never seen any of these methods or any combination of them result in a cure that could not be attributed to time alone, though I do not doubt that such cures have been achieved. Even the vaunted removal to the dry warmth of the southwestern United States seems on the whole more apt to relieve the harrassed dermatologist than the distressed patient.

William Guy Jr and associates at the University of Pittsburgh have reported encouraging progress in the investigation and attempted psychiatric management of adult atopic eczema.* They have recently reported group psychotherapy to be effective, though it was not acceptable to all cases. Eight patients (in a group of 25 of whom 17 were evaluated) achieved increased verbal and physical aggressiveness and a (resultant?) change in their social relationships and were significantly improved, so were three who withdrew from the group in open anger Of the six who did not improve, four had withdrawn from the group without open expression of hostility or resentment, and two had merely failed to show any change as a result of the group experience

Severe long-standing disseminated neurodermatitis usually constitutes a valid indication for the oral administration of cortisone or hydrocortisone. This is a radical step often an irrevocable one, and not to be taken lightly The most serious risk, perhaps, is that of lighting up a latent tuberculosis or peptic ulcer

Cushing's syndrome in whole or in part, moon face, acne, hirsutism, diabetes mellitus, hypertension, and so forth, is neither a very common nor a very serious complication of corticoid therapy Demineralization of bone has not been a problem in our cases, either though on theoretical grounds it is likely to occur.

leum jelly I decided that she was suffering from acute exudative neurodermatitis, as her previous attendant had suspected, and told her I thought psychiatric help was urgently indicated. She agreed enthusiastically stating that she was a bundle of conflicts. By this time she was tolerating an ointment, the base of which was composed of petroleum jelly cold cream and lanolin in equal parts, without any reaction.

The psychiatrist who saw her after a brief preliminary inquiry informed her that he had practiced a little dermatology before he took up psychiatry and that he thought he knew what would clear her up namely Crisco (a solid proprietary hydrogenated cooking fat) This was applied to her lesions, and within two days she had cleared enough to leave the hospital.

Within another month she had divorced her husband, who subsequently married the Oriental girl he had been in love with since shortly before his wife s dermatitis began. There was no recurrence up to six years later

SUMMARY

Pruritus, like erythema, may have its origin either in the skin or in the hypothalamus. When it occurs exclusively in paroxysms of irresistible severity occurring chiefly during moments of leisure or sleep and is relieved only by pain, it probably has its origin in the hypothalamus, and the treatment should ideally be applied where the trouble is.

It has been suggested that the combination of a dermatologic and a psychiatric approach to the management of these cases is undesirable, in that each may tend to undermine the patient s confidence in the other so that the patient falls, as it were, into the gap between the two and is benefited by neither It may be that there is some truth in this view The adventitious psychotherapeutic effect of the patient s confidence in and dependence on the dermatologist and the dermatologic medications is probably diminished (if the patient is referred to a psychiatrist) by the realization that the dermatologist himself does not have complete confidence in his own approach. It may be that the same criticism applies though with somewhat less force to the effect of concurrent dermatologic treatment on the psychiatrist s efforts.

It has been my practice for this reason, to withdraw from the

scene as nearly completely as possible when I have referred a patient to a psychiatrist and to emphasize topical therapy as little as possible when I am conducting psychotherapy myself. This is a question for which there can be no hard and-fast answer: each case must be judged and managed on its own merits.

It has been objected that there is no sound scientific basis for attributing these diseases directly to emotional causes and indeed there is very little. It is in the nature of the problem that there *should* be very little. Most of psychiatry is based on inferences from the most inexact and complex sort of data. This portion of it is no exception. The kind of evidence from which we draw conclusions about bacterial and metabolic diseases is simply not available to us in psychogenic disorders. It is a sterile and futile sort of skepticism that insists, because of this, on denying that we can attribute physical disorders of the skin to emotional causes.

It was a hundred years ago that Forbes Winslow summarized in the First Lettsomian Lecture what we believe today about psychosomatic illnesses. "Many a disease," he said, "is the *contre coup* so to speak, of a strong moral emotion, the mischief may not be apparent at the time, but its germ will nevertheless be laid." And as Henderson said, in commenting on Winslow's views, "Man's reaction to man may be at least as important as his reaction to a microbe."

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7

Comparative Pathogenesis of the Deep Mycoses

THE INFLUENCE OF THE PORT OF ENTRY

By
J Walter Wilson

It has long been emphasized that each of the category usually referred to as the "deep mycoses" presents a clinical course remarkably different from the others, the total of these differences conferring upon the group as a whole the ability to duplicate almost any combination of the signs and symptoms of chronic disease. Because of this variability it is necessary to include fungous disorders such as these in the differential diagnosis of any chronic condition whose pathogenesis seems obscure. Well-known are the peculiar predilections of histoplasmosis for the reticuloendothelial system, of cryptococcosis for nervous tissues, of North American blastomycosis for the skin, and of sporotrichosis for the lymphatic structures of a single limb Also it is remarkable that South American blastomycosis consistently selects the oropharyngeal and gastrointestinal tract as assiduously as coccidioidomycosis avoids it.

Some of these differences are undoubtedly attributable to certain inherent preferences on the part of the fungi for special environmental features for example the deep seated nature of actinomycosis is, in part at least, a reflection of the desire of the fungus for anaerobicity The persistent refusal of viruses to grow extracellularly makes the same proclivity of Histoplasma capsulatum easy to accept, and it is logical to allow Cryptococcus neoformans the same privilege of preference for nerve tissues that we do the causative organism of rabies.

In the midst of such outstanding individual variability among the deep mycoses, there are, however certain threads of similarity

the study of which offers theories apparently capable of explaining certain of the less commonly encountered manifestations hitherto regarded simply as more or less "atypical." In fact, it seems likely that such concepts may furnish clues of great value in the study of infectious diseases in general. In this paper one such train of thought is to be pursued, consisting of an analysis of the importance of the port of entry of the fungus causing a deep mycosis.

Excluding for the moment their unusual manifestations, coccidioidomycosis and sporotrichosis each presents a typical form the two clinical pictures are, however perhaps as different as those of any other pair of diseases which could be selected. The former infection is acquired by nearly all exposed persons, but so mildly that most of them remain entirely unaware of its presence while a spontaneous cure occurs, conferring subsequent immunity to reinfection. Most of the remainder finally achieve the same result but only after a variable amount of clinical illness center ing about the lungs, while a very few sustain a widespread disseminated chronic granulomatous disease highly dangerous to life itself Conversely sporotrichosis typically results in a chancriform syndrome, represented by an initial ulcerative papule accompanied by acute lymphangitis and nodules along the lymphatic vessels draining that area and regional lymphadenitis, the entire process usually remaining limited to the affected extremity with virtual exclusion of dissemination into a fatal form.

The most logical reason which comes to mind for such a marked difference in their clinical appearance is that these two infections are acquired in entirely different manners through different ports of entry and that they primarily involve different tissues. It has long been recognized that coccidioidomycosis is almost always acquired by the inhalation of the arthrospores of the fungus along with windborne dust, resulting in a primary pulmonary infection sporotrichosis is equally predominantly acquired by the inoculation of the fungus through the skin by a puncture wound. It is at once obvious that with such a difference in the ports of entry the typical forms of the two disorders must differ accordingly While other factors may also be somewhat influential, it is not necessary to invoke them to explain adequately this phenomenon.

Having disposed for the moment of the typical forms of these two diseases, let us now consider whether or not this theory can account also for their more unusual manifestations. What happens if these routes of infection are reversed? First, what is the result of intracutaneous inoculation of C immitis? Throughout the years there have been a few cases of coccidioidomycosis which first appeared as a lesion of the skin, without evidence of previous pulmonary involvement, usually beginning as a subcutaneous nodule which soon became ulcerative and persisted as a slowly enlarging chronic granulomatous plaque, without any lymphatic sequelae. This was frequently followed by other similar lesions elsewhere on the skin. It was usually concluded that this clinical picture was due to the fungus having been inoculated directly into the skin, although in no recorded instance was this supported by adequate proof, many such cases lacking even the history of any cutaneous wound. Nevertheless, this syndrome came to be considered the expected result of direct cutaneous inoculation of Coccidioides, (the so-called primary cutaneous form)

Although it is shameful to have to admit such careless technique, defensible only in that it is in the tradition of the Western pioneers to live dangerously it is nevertheless a fact that within the last six years there have been in Southern California three instances of known accidental intracutaneous inoculation into human beings of fungi capable of causing deep mycoses; one each of C. immitis, Blastomyces dermatitidis and Blastomyces brasiliensis all of which cases I, among others, have been privileged to observe and follow

The first of these involved a mortuary attendant who, while preparing a body heavily infected with Coccidioides, allowed pus to enter a deep abrasion on his finger Subsequently he presented a clinical picture in no way resembling that which previous opinion would have led to be expected but instead entirely typical of that seen in the usual form of sporotrichosis, differing only in that Coccidioides was cultured and demonstrated histopathologically instead of Sporotrichum. He recovered spontaneously and has remained free of recurrence.

While it is admittedly unwarranted to draw conclusions from the observation of a single case, the fact that this is the only

was recovered on culture plates exposed to air currents only once out of many attempts. From these considerations it is easy to understand the almost invariable entry of this fungus into the human body by way of a cutaneous puncture wound, with only an occasional instance of pulmonary invasion.

If a new theory be valid, additional support may be obtained by testing its ability to clarify other previously unexplainable phenomena. It is helpful, therefore, to consider next the influence of the port of entry of the organism upon North American blastomycosis. Very shortly after its discovery it became evident that this disease occurs in two widely divergent forms one an acute or subacute granulomatous infection centering about the lungs and tending soon to become widely disseminated, usually causing death, the other consisting of a lesion or lesions apparently involving the skin alone in a chronically progressive, ulcerative, granulomatous, and cicatrizing process, usually persisting over many years without affecting the general health of the patient. It became widely accepted that this sharp differentiation occurs entirely because of different ports of entry· inhalation of the fungus causing the pulmonary type and its inoculation directly into the skin resulting in the chronic cutaneous form. As was the case with coccidioidomycosis, however in all recorded instances of the chronic, cutaneous form, this direct cutaneous inoculation was only assumed, never proved conclusively In fact, the reservoir in nature of this fungus still remains obscure.

As early as 1903, Evans reported that "a pathologist of my acquaintance" (actually Evans himself) had sustained a needle puncture wound in a finger during the performance of an autopsy upon the body of a person dead of blastomycosis. This was followed by the development of a syndrome differing entirely from the chronic cutaneous form of blastomycosis expected by prevailing opinion. Instead, it was chancriform and identical with that typical of the common form of sporotrichosis.

In 1927 Weidman sustained a similar inoculation from a laboratory culture and observed the same phenomenon. Then, in 1952, in the course of an extensive study of blastomycosis, Schwarz and Baum concluded that the usual so-called "chronic cutaneous form does not originate from intracutaneous inoculation but ac-

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instance which resulted from a proved intracutaneous inoculation should cause it to be given great weight when considered against the evidence assembled in those cases in which such a route was only surmised. When, in addition, it is pointed out that the same type of cutaneous involvement as that previously supposed to result occasionally from cutaneous inoculation has been observed repeatedly when the lungs were known to have been the primary locus it becomes logical to ascribe all such cases to a similar mechanism. Thus it appears likely that when inoculated directly and primarily into the skin of previously uninfected persons Coccidioides and Sporotrichum produce identical chancriform syndromes.

What happens when sporotrichosis is acquired by a route other than its usual cutaneous inoculation? While a benign form of pulmonary involvement has not yet been described, cases of disseminated sporotrichosis have been occasionally observed. The clinical picture bears many similarities to disseminated coccidioidomycosis, exhibiting multiple subcutaneous nodules and abscesses and verrucous plaques as well as pulmonary bone, and visceral involvement, terminating frequently in death.

The manner of entry of the fungus in these cases has usually been unproved, but it is presumed to be either by inhalation or ingestion. That it probably never results from primary cutaneous inoculation may be concluded from the fact that it was not observed at all in the series of 1,471 cases occurring in the South African mines under conditions in which the skin was almost certainly the only port of entry Also, in none of the American cases of disseminated sporotrichosis reviewed by Collins was the port of entry known to have been the skin. Likewise in France, where the disseminated form occurs more frequently a proved primary cutaneous lesion has not been observed to precede it.

Since the reverse appears to be even more unlikely if not impossible, (for a chancriform syndrome to result from an inocula tion elsewhere than into the skin) we may logically conclude that when Sporotrichum infects the human body by a route other than *the skin, the resulting syndrome resembles disseminated* coccidioidomycosis much more than it does conventional sporotrichosis.

It is thus evident that most, if not all, of the extensive apparent

variations between coccidioidomycosis and sporotrichosis may be explained on the basis of the difference in the port of entry and that when this influence has been appropriately evaluated the two diseases are closely similar It is indeed surprising how little variation remains unexplained by this thesis, especially when it is recalled that in the infected tissues the two fungi bear no resemblance to each other and call forth entirely different histopathologic responses. It would, indeed, be strange if the diseases resulting from such dissimilar organisms were entirely alike.

In artificial culture at ordinary atmospheric temperatures, (conditions under which these two fungi maintain themselves in their natural reservoirs) they exhibit characteristics which make it easy to understand the above variation in their selection of ports of entry into the human body

C. immitis grows as a fluffy filamentous colony resembling cobwebs, much of which is composed of specialized hyphae segmented by fragile cross walls into arthrospores with a narrow collarette between them These spores break apart from one another with extreme ease, allowing the smallest air current to detach a cloud of them from the surface of the colony They are so light that they are easily borne on the wind for great distances. By the same token these infectious elements cannot cling very tenaciously to the surface of materials capable of inflicting puncture wounds into the skin, so that no large numbers of them could be implanted deeply by such a means. It is therefore entirely logical to find that this infection is almost always acquired by the inhalation of the fungus to the virtual exclusion of the intracutaneous inoculation route.

Conversely S schenckii grows typically as a moist mat of densely interwoven filaments closely applied to the surface of the medium, in nature it prefers materials capable of furnishing thorns and splinters such as vegetation and wood, into whose crevices it extends itself presenting no dry aerial cottony elements which air currents might easily remove. It is admittedly true that the spores are attached to the hyphae by fragile threadlike sterigmata, so that if the entire culture and its substrate be dried, such spores may become windborne. This rarely happens, however, since in an environment where it was present abundantly Sporotrichum

was recovered on culture plates exposed to air currents only once out of many attempts. From these considerations it is easy to understand the almost invariable entry of this fungus into the human body by way of a cutaneous puncture wound, with only an occasional instance of pulmonary invasion.

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tually results instead by dissemination from a preceding primary pulmonary infection, frequently unrevealed unless searched for carefully. This view was corroborated by Wilson, Cawley, Weidman, and Gilmer who reported two new cases of known intracutaneous inoculation followed by the chancriform syndrome so typical of sporotrichosis. (One of these was alluded to previously as the second of the Southern California inoculations with deep mycotic organisms.)

It seems logical to permit the facts assembled in the observation of these four cases, in which the chancriform sporotrichotic syndrome followed *an infection with Blastomyces which was known* to have been acquired by the intracutaneous route, to outweigh the significance of the larger number of previously recorded cases in which the chronic, cutaneous form was observed and which were attributed to an intracutaneous inoculation by assumption only. Furthermore, it is easy for me to accept the opinion of Schwarz and Baum that the chronic cutaneous form is simply the residual of blastomycosis disseminated from a previously unrecognized primary pulmonary focus, since almost the exact counterpart, *although admittedly more dangerous to life, occurs in coccidioidomycosis.*

Upon reflection, the reader may find it difficult to accept cutaneous blastomycosis enduring for many years as only another manifestation of disseminated disease from a preceding pulmonary focus. Why does not a high percentage of such patients die of visceral involvement? It is necessary to point out that there is considerable support for the view that the viscera resist the disease more efficiently than the skin and succeed in entirely eliminating the infection, whereas the skin never quite succeeds. This view seems entirely logical when one recalls the histopathologic picture of this chronic, cutaneous form of blastomycosis, consisting of a tremendous cellular infiltrate contributed by the host in response to an extremely rare blastomycete, thousands of the former to one of the latter.

The very size of the infiltrate indicates that a terrific battle is being waged against the infection, a battle not completely successful because of some immunologic defect. This view also furnishes an explanation for the fact that the chronic cutaneous form

can endure for decades without dissemination, the viscera having already successfully thwarted the dissemination which caused the skin lesion in the first place and having learned how to resist any such tendency as might occur again. The prognostic significance of the interplay between skin and complement fixation tests fits this concept also: in fact some of the apparent inconsistencies of the interpretation of such reactions are adequately explained thereby even as they are in coccidioidomycosis.

Before proceeding to apply this thesis to the other deep mycotic infections it is necessary to point out that in blastomycosis it is also beautifully supported by certain immunologic and serologic phenomena too complicated for a detailed analysis here. In fact, this is not an unidirectional contribution for this theory in turn adequately explains several hitherto puzzling aspects of the intradermal, precipitin, and complement fixation reactions to coccidioidin and blastomycin and seems to promise similar results in the study of sporotrichin and histoplasmin. This subject will be treated more intensively in a later article

All of these observations, clinical as well as mycologic and immunologic, indicate that for the chancriform syndrome to develop, the body of the host must actively resist the infection and its progress to a considerable degree either by immunologic, allergic, or cellular processes. This does not mean that such resistance will necessarily be efficient enough to result in complete eradication of the infection, in fact, in almost all diseases it is not, being followed either by a prolongation of the localized lymphatic involvement as in sporotrichosis or the development by dissemination of secondary lesions elsewhere in the body as in syphilis yaws, and leishmaniasis. Nevertheless the chancriform syndrome itself appears to be an essentially benign process in all diseases in which it occurs. Thus the primary cutaneous complexes of coccidioidomycosis, sporotrichosis, blastomycosis, syphilis, tuberculosis yaws and American leishmaniasis are parallel, being in themselves essentially self limited, although serious sequelae may follow

The chancriform syndrome has not been reported to occur in deep mycotic infections other than the three already discussed, similarly no instances have been recorded in which direct cutane-

ous inoculation of such causative fungi into human beings has been conclusively proved. Failing experimental procedures in man (or in animals which might eventually be shown to resist the infections in the same manner) we can only speculate as to the results of such inoculations.

The author has observed one instance of known intracutaneous inoculation of Blastomyces brasiliensis into a laboratory worker's finger by a hypodermic needle. Two days later a papule was seen, which was removed by a biopsy punch with subsequent fulguration of the wound. Healing was uneventful and there have been no sequelae during the ensuing three years. Histopathologic examination revealed the organisms in their typical tissue form, giving every appearance of viability and reproduction, but culture was unsuccessful. Whether they were in fact avirulent, implanted in insufficient quantity or surgically removed too soon to afford a conclusive test cannot be stated. Not enough is yet known as to the immunologic status of this disease in human beings to speculate further

Histoplasmosis follows the immunologic pattern of coccidioidomycosis so faithfully in those phases which are thus far understood, that it may be predicted that if it were acquired by the intracutaneous route, a chancriform syndrome should develop Curtis and Harrell have observed a case not yet reported in which a penile chancre with regional lymphadenopathy was shown to be caused by histoplasmosis, the disorder slowly subsided and did not recur Curtis and Harrell believe it probable that the fungus was inoculated into the skin in this instance. Conversely the granulomatous lesions of skin and mucous membrane which have been observed in other cases were probably the result of dissemination from a primary pulmonary infection

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8

Latin American Contributions to Medical Mycology with Special Reference to Maduromycosis

By

Irene Neuhauser

CONTRIBUTIONS to medical mycology from Latin American research centers have most frequently appeared in the Spanish and Portuguese languages and in journals having a limited circulation beyond the countries in which these languages are spoken. As an unfortunate consequence, Latin American scholarship has been inadvertently underestimated among those workers whose attention is more readily attracted to studies in English, French, or German. Further the very laudable desire of Latin American investigators to encourage development of serious scientific journals in their own countries has caused them to sacrifice the wider and more rapid dissemination and appreciation which translation and publication abroad would have assured their papers.

Studies of mycotic diseases and their causative agents which have come from Latin America have an increased importance because of peculiarities associated with these diseases. The etiologic agents may be carried as surface saprophytes or be introduced into the host from exogenous sources. The diseases are sporadic and are rarely transmitted from individual to individual. The circumstances underlying the infections remain obscure. Much information must be obtained on the incidence and distribution of these diseases the racial, economic, nutritional, and hygienic backgrounds of the patients and the morphologic and biologic peculiarities of the organisms.

Latin America has a rich mycologic history Investigations

published a number of papers on the superficial and deep mycoses and the latter is known for his studies on the differentiation of the monilias and for the introduction of media containing actidione as a new mycologic technique.

It must not be assumed that the failure to mention individuals and contributions from other countries implies that no contributions of value are being reported or that competent mycologists are not actively engaged on problems of clinical and scientific interest. Although the limited amount of space available for this chapter makes it impossible to include much work of value, Delamare and Gatti in Paraguay Iriarte in Venezuela, and Trejos in Costa Rica must be mentioned among Latin American mycologists who have attracted serious attention beyond their own countries.

Scientific disciplines are nourished in the soil of intellectual cooperation. Historically medical mycology in both North and South America looked to European leadership and a certain amount of mutual interchange of ideas and appreciation of personalities came about between the two hemispheres through European mediation. With the realization that the tasks of medical mycology in North and South America are different though closely related, necessary specialization naturally developed. This has tended to bring about a certain degree of isolation which has only partly been overcome by the publication of abstracts and by the interchange of students. In the majority of instances it has been the Latin American scholar who has come to North America and acquired an understanding of our language and our intellectual ambient through close contact with our scientific personalities. It is important that North American scholarship should be represented by a much larger group of students in Latin American research centers and that the importance of a good reading knowledge of Spanish and Portuguese be stressed in the preparative years of those who plan to make medical mycology a life work.

The work of Mackinnon and coworkers, in Uruguay represents an important recent advance in medical mycology

The historical data on the subject of maduromycosis were so excellently reviewed by Chalmers and Archibald, in 1916, and by Gammel, in 1927 that only a brief historical summary is necessary for explanation of terms used in the published literature.

In 1842, Gill of the city of Madura, India described as an entity a peculiar disease of the foot which had been seen in that area. The disease was characterized by marked deformity of the foot, accompanied by discharge of a fetid liquid and by destruction of joints, cartilage, and ligaments Colebrook, in 1846, in the same city introduced the name "madura foot by which the disease was locally known. In 1858, Rustomji noted the presence of black and yellow granules in pus from "madura foot." The term "mycetoma was proposed by Carter to designate fungous infections of the subcutaneous tissues characterized by swelling, formation of sinuses and production of pus containing well organized granules. Carter also noted that the granules differed in size, shape, and color

The relationship of several species of fungi to cases of mycetoma was discussed by Brumpt. In 1913, Pinoy proposed a division of the maduromycoses into the actinomycoses caused by species of actinomyces and the "true mycetomas caused by fungi characterized by broader hyphae. Chalmers and Archibald substituted the name maduromycosis for "true mycetoma," and this name has persisted to the present time

To date, ten species of madurella have been described in addition to species in other genera of the class Fungi imperfecti and the class Ascomycetes as causative organisms in maduromycosis.

Until lately little real progress had been made in our knowledge of the causative organisms of maduromycosis. A great deal of the published work is incomplete or insufficiently detailed to permit the determination of the species. This has been due, in part, to the lack of adequate media for cultivating the organisms and to insufficient mycologic training on the part of those reporting on this subject. Progress has been particularly disappointing in the characterization and identification of certain species causing black grain maduromycosis, because the organisms lack the morphologic forms which make botanical identification possible.

The recent clarifying work on the black grain maduromycoses has been largely due to Mackinnon and coworkers. Their investigations have embraced the black and white grain types, but they have been particularly valuable in providing a sound and workable classification for the organisms causing the black grain types.

Since classification on morphologic data alone has not been possible in this group Mackinnon included procedures which were based on the nutritional requirements of the organism. He applied these criteria to all available cultures of the organisms causing maduromycosis. The procedural steps in Mackinnon's scheme of classification involve the following:

1. Gross appearance of giant colonies of the fungus on Sabouraud's glucose agar after forty days at 27 to 30 C.

2. Appearance of slide cultures grown on soft agar medium containing 2 per cent of glucose and 1 per cent of peptone.

3. Determination of the optimal growth temperature by incubation of cultures at 37 C., 27 to 30° C and at room temperature in summer (18° to 30 C.)

4 Study of the utilization of nitrogen by the organism. For this purpose Mackinnon used media having nitrogen available as urea, asparagin, ammonium sulphate, and potassium nitrate.

5 Study of the utilization of carbon by the organism. For this purpose Mackinnon used media containing available carbon as glucose, maltose, galactose, lactose, and sucrose.

6. Determination of the proteolytic activity of the organism by growing it in milk and gelatin and on Loeffler's media.

7 Determination of the amylolytic activity of the organism by testing its ability to hydrolyze starch.

Utilizing the data obtained from the testing procedures mentioned, Mackinnon was able to identify a new species of Madurella, which he named Madurella grisea. Carefully analyzing the data from tests on all available cultures of organisms known to have caused maduromycosis he has been able to develop a very useful systematic classification of these organisms, ending the *chaotic situation which has existed for many years.* Although the original publications by Mackinnon and coworkers should be studied by those who have a serious interest in this field, a brief résumé of the classification may be helpful to others.

CLASSIFICATION OF BLACK GRAIN MADUROMYCOSES ACCORDING TO MACKINNON

Type I. These strains form colonies consisting of an ochreous mycelial growth covered by a short white pubescence which turns

yellow or ochre. A brown pigment is produced. The organisms of this group utilize lactose but not sucrose. Their optimal temperature is about 37 C This group comprises M americana (Gammel 1926) M. ikedae (Gammel 1927) M tonzeuri (Nicolle and Pinoy 1912) and cultures submitted under the name of M mycetomi.

Type II. This type produces hard colonies composed of a nearly black mycelial mass covered by a grayish aerial growth which turns brown in old cultures. These strains utilize glucose, maltose, galactose, and sucrose but not lactose. They develop best at 30 C. This group comprised the strains named M grisea.

Type III. Phialophora jeanselmei is the sole representative of this type. It is a nonthermophilic species which produces soft black grains formed by hyphae which are not united by a pigmented mass. Typical conidia are abundant. The optimal temperature for growth is 30 C.

Type IV Comprised by Glenospora clapieri, this thermophilic species utilizes glucose and peptone as sole sources of carbon and nitrogen respectively

Type V This type consists of one species Monosporium sclerotiale which grows best at 25° C. It utilizes the five test sugars, glucose, galactose, maltose, lactose, and sucrose as sources of carbon, and peptone, asparagin, urea, sodium and potassium nitrate, and ammonium sulfate as sources of nitrogen.

Further work now in press has been carried out by Mackinnon in an attempt to differentiate the types of maduromycosis by the appearance of the parasitic grains. If these procedures are successful, clinicians will have a ready means of identifying the organisms which can easily be carried out with limited facilities.

Any attempt to sketch in broad outline the historical development of a science and to evaluate the work of those who have made important contributions to it must suffer from the personal interests and deficiencies of the author This is true even when circumstances permit an exhaustive and detached treatment of the subject. The author is keenly aware that much work of importance in medical mycology remains unreported in this chapter and that errors in judgment and appraisal have certainly been made. These have been entirely unintentional and in no way re-

flect on any one except the author It is hoped in spite of these deficiencies that this brief review may be found useful by those in English speaking countries who may be unfamiliar with the Latin American mycologic literature and the distinguished workers who have created it.

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On the positive side, with the notable exception of Mackinnon's procedures based on the nutritional requirements of the fungus and the appearance of the parasitic granules, there are precious few features of practical significance which can aid us in the differentiation of species and genera responsible for mycetomas.

Chemotherapy of actinomycotic and maduromycotic infections has been extremely discouraging However the excellent results recently obtained by Mexican dermatologists in the treatment of anaerobic and aerobic actinomycotic infections with diaminodiphenyl sulfone (DDS) have favorably changed the prognosis

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9

Coccidioidomycosis

(POSADA'S DISEASE)

By
Pablo Negroni

COCCIDIOIDOMYCOSIS is endemic in the arid and semiarid lands of America, where it is contracted by persons inhaling dust laden with the causative agent of the disorder Coccidioides immitis. The fungus is a natural inhabitant of the soil of endemic areas extending from California in the north to Patagonia in the south. In North America, this region embraces the vast basin of the Colorado river stretching from the Rocky Mountains in the east to the Sierra Nevada mountains and those comprising the coastal range in the west, thus encircling the states of California, Arizona, Texas, and New Mexico. Recent surveys indicate however that the infection is spreading to neighboring states, probably due to its dissemination in vehicles and luggage, by those travelling in and out of the endemic zones

Gonzalez and his collaborators state that lower California and Puerto San Felipe constitute infected localities in Mexico. Corrales-Padilla, and Castro and Trejos, independently reported the first instance of the disease in Central America, the patient being a resident of the Comayagua valley of Honduras.

Campins found 46.4 per cent of the inhabitants of the state of Lara in Venezuela reacting strongly to the intracutaneous test with coccidioidin, and *Lasso-Meneses observed positive reactions* in 6 per cent of the people of Pomasqui, a town situated near Quito in Ecuador Gomez, in the northern Paraguayan Chaco obtained a positive response to intracutaneous testing in 43.9 per cent of the inhabitants. In Argentina, my collaborators and I

flect on any one except the author It is hoped in spite of these deficiencies that this brief review may be found useful by those in English speaking countries who may be unfamiliar with the Latin American mycologic literature and the distinguished workers who have created it.

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EDITOR'S COMMENT

As Neuhauser showed in the preceding chapter, the studies of Mackinnon are helping to clarify the chaotic situation which has existed for many years in the classification of the organisms causing maduromycosis. As one travels throughout the Americas, it becomes increasingly evident that there is a great need not only for simplification of the taxonomy of the fungi causing maduromycosis but also for reduction to synonymy of such terms as actinomycosis, nocardiosis, maduromycosis, and mycetoma.

The great number of synonyms for each fungus is also a source of confusion to workers in different countries. For example, the

most fully described species of Central and South America, N brasiliensis, is also described by Mexican mycologists as Actinomyces mexicanus and Discomyces brasiliensis. Most North American mycologists recognize the following four species of the genus Nocardia N brasiliensis, N asteroides N pelletieri and N madurae (A. micetomae)

A differentiation of species and genera based on the color of the granules is unfeasible for several reasons. The granules of the aerobic actinomycetes, for instance, are often yellowish-white or grayish-white, but this feature does not enable us to distinguish between the genera Actinomyces and Monosporium apiospermum.

This difficulty was evident in three patients with Madura foot recently observed in the clinic of Dr Pardo-Castello in Cuba. The grayish-white granules expressed from the fistulae of two of these cases were studied by Dr Trespalacios. When planted on Sabouraud's glucose agar at 37° C., the granules increased in size until in two weeks time they developed into coral red colonies which microscopically showed the typical features of N pelletieri.

The other patient produced yellowish white granules which are customarily regarded as characteristic of aerobic Actinomyces The grayish-white, powdery colony developing from these granules, however showed features of Monosporium apiospermum.

Furthermore, according to Conant and his associates, a classification based on the pigmentation of the granule is not feasible because of the variety of cultures obtained when granules of the same color are cultured. These same authors also point out that certain atypical mycetomas are characterized by a total absence of granules.

The problem is further complicated by the observations of Trejos and others. After studying the mycologic features of cultures labeled "Candida-like sp. de Berger (Torula bergeri) submitted by Carrion, Trejos stated that he studied Torula bergeri isolated by Berger and his coworkers in Canada and felt that there were no specific differences between this fungus, which produced chromoblastomycosis, and Phialophora jeanselmei, one causative agent of mycetomas. Therefore he considers Torula bergeri as synonymous with Phialophora jeanselmei."

Furthermore, the studies of Hansen and Lindner should be recalled in this connection. These authors according to Skinner and his associates, showed that " black yeasts are but yeastlike growth forms of dematiaceous molds of the type of Cladosporium " This concept, taken in conjunction with Trejos belief in the synonymy of Torula bergeri and Phialophora jeanselmei, two fungi which were previously considered as two distinct causative agents of chromoblastomycosis and maduromycosis, respectively immeasurably expands the category of possible etiologic agents of not only maduromycosis but also of other deep mycoses.

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9

Coccidioidomycosis

(POSADA'S DISEASE)

By
Pablo Negroni

Coccidioidomycosis is endemic in the arid and semiarid lands of America, where it is contracted by persons inhaling dust laden with the causative agent of the disorder Coccidioides immitis. The fungus is a natural inhabitant of the soil of endemic areas extending from California in the north to Patagonia in the south. In North America, this region embraces the vast basin of the Colorado river stretching from the Rocky Mountains in the east to the Sierra Nevada mountains and those comprising the coastal range in the west, thus encircling the states of California, Arizona, Texas, and New Mexico Recent surveys indicate, however that the infection is spreading to neighboring states, probably due to its dissemination in vehicles and luggage, by those travelling in and out of the endemic zones.

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Campins found 46.4 per cent of the inhabitants of the state of Lara in Venezuela reacting strongly to the intracutaneous test with coccidioidin, and Lasso-Meneses observed positive reactions in 6 per cent of the people of Pomasqui, a town situated near Quito in Ecuador Gomez, in the northern Paraguayan Chaco, obtained a positive response to intracutaneous testing in 43.9 per cent of the inhabitants. In Argentina, my collaborators and I

uncovered the existence of an infected area extending along the Andean slopes from the Rio Hondo and the western limits of the city of Santiago del Estero in the north to the Rio Colorado in the south, the incidence of positive reactions in this region varying between 10.28 and 19 72 per cent.

Infection occurs in a great majority of all persons within a few months or years of residence in one of these endemic areas owing to inhalation of dust containing the fungus in the form of thallospores provided with membranous appendages enabling them to float in the air A large percentage of these individuals are completely unaware of the infection, yet they show cutaneous sensitivity to the skin test with coccidioidin, later acquiring immunity

The infection becomes evident after an average incubation period of 15 days as an illness varying in intensity from mild respiratory symptoms to severe pulmonary and pleural involvement. This so-called primary infection is frequently accompanied by conjunctivitis, joint pains, and eruptions simulating nodose and multiform erythema, wherefore the disorder is popularly known in the United States as San Joaquin valley fever or rheumatism. Generally patients recover completely from this benign form of the disorder in one or two weeks, although there are always some who are left with a residue of small calcareous deposits in the lungs.

Disseminated coccidioidomycosis occurs weeks or even months after the primary infection in approximately one in 500 individuals with involvement of possibly all the organs of the body Of these, the skin, connective tissue, bones, joints, and central nervous system show the most frequent alterations.

The cutaneous changes occurring in these patients begin as small, reddish brown, smooth papules that soon become pustules, breaking down to form ulcerating and vegetating lesions resembling those of blastomycosis. They are currently regarded as metastatic manifestations and may or may not be associated with flaccid swellings, cold abscesses or gummatous lesions of the subcutaneous tissue Jacobson states that scrofulodermatous lesions show a preference for the neck and skin above the clavicles. Along with Fitte I have occasionally observed the formation of mycetomalike lesions on the lower extremities, where the infec-

tion first affects the joint tissues and later invades the soft parts, building fistulas on the outside.

In soil and on artificial media, C. immitis grows as a branching septate hyaline mycelium, from which proconidia develop as precursors of thick walled, spherical, rectangular or ellipsoidal thallospores (entospores)

When these "entospores" enter or are injected into human beings or animals, they first swell and transform into sporangia. Photographs of my experiments show these sporangia attaining a diameter of 94 microns and possessing a thin membrane, along which endospores containing granules dispose themselves in a peripheral band of fertile protoplasm. A lagoon of residual protoplasm fills the center of the spherule. Dehiscence takes place by endospores passing through an ostiole measuring 6 microns across, after which they are ready to begin a new life cycle. The empty spherule is invaded by white blood corpuscles and resembles the nonbudding form of B dermatitidis.

The host acquires specific immunity after the second week of the infection, thereby producing fungistasis which is implemented by the phenomena of retarded development and encystment of the organism. The retarded development of the organism can be demonstrated microscopically by the reduction in size of the spherule to 35 or 40 microns in diameter and by the disappearance of the central lagoon of residual protoplasm and ostiole. Large spores now pack the entire spherule.

The encystment of the fungus proceeds simultaneously and is finally accomplished by thickening of the peridial membrane, with the production of radiating acidophilic spines surrounding a cystic spherule. The ultimate destruction of the organism is consummated by giant cells. The time required for an endospore to pass through all of the transitional forms from a primary sporangium to a sterile cystic spherule is about two weeks.

The histiologic appearance of skin lesions is closely related to the state of immunity In the early stages of the infection, before specific immunity has been acquired, histiologic sections show inflammatory changes with the production of polymorphonuclear abscesses. The parasites are found free and in large numbers After the second week, proliferative changes occur with the for

mation of a granulomatous infiltrate usually containing a few giant cells.

The diagnosis of coccidioidomycosis can only be established by mycologic methods of examination, it being sufficient to find typical sporangia in the lesions. The white, cottony aerial mycelium, that develops on incubation of the fungus on blood infusion broth agar at 30 C. in eight days, is characteristic and easy to obtain, the inoculation of this culture material into guinea pigs producing histologic changes similar to those induced by the tubercle bacillus.

Coccidioidin is a sterile filtrate of cultures of the organism, grown in a liquid mineral medium that is practically protein free. A positive reaction exhibited by persons to the intracutaneous injection of this antigen in dilutions of 1 100 indicates that they are either acquiring hypersensitivity in the course of an actual infection or that they have been previously infected and have recovered with permanent immunity These individuals show hypersensitivity by responding positively to the test for many years. It is best to use dilutions of 1:1000 in suspected instances of the disorder in order to avoid severe focal and systemic reactions. In my studies conducted on persons residing in endemic areas, a dilution of 1 100 was used, and the reaction, if any was read after 36 hours, as in the manner of old tuberculin.

The complement fixation test has prognostic value, becoming positive much later than the intracutaneous test and showing a negative response when the disease is cured, so that a persistence of positivity implies that the individual has failed to acquire immunity and that dissemination of the infection has taken place.

My collaborators and I believe that irrigation provided by the construction of dams in endemic areas constitutes the best method of stamping out the disease, the desert zones being thereby transformed into cultivated lands free from parasites.

The management of patients in the acute stages of primary coccidioidomycosis consists of bed rest and the administration of water soluble vitamins. There is no effective treatment at present for the disseminated form, although there are certain antibiotics, such as chloramphenicol and prodigiosin, that exert an inhibitory action in vitro on C. immitis.

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10

Sporotrichosis

By

Elias Bonilla-Dib

SPOROTRICHOSIS is a granulomatous disease which may be acute, subacute, or chronic. It is caused by Sporotrichum schenckii.

S schenckii is the sole etiologic agent of the disease, the different species and varieties described as causing the disease merely representing structural alterations during the growth of S schenckii on artificial media. It has been demonstrated that a single strain of the fungus is capable of producing several varieties after repeated culturing

The disease has a world wide distribution among all races. It shows distinct seasonal tendencies, occurring most commonly in young men at the time they collect sugar cane and other crops. Gardeners, florists, and field workers are particularly susceptible, especially when handling plants, contaminated material and when coming in contact with animals acting as mechanical carriers.

The infection is often from occupational trauma, as in Mexico where potters commonly contract the disorder from handling contaminated straw in packing their wares. In Costa Rica, workers in the cane fields as well as carpenters handling contaminated wood show a high incidence of infection. The report of almost 1500 cases of the disease occurring in South African miners working in galleries made of contaminated wood has become a classic.

SYMPTOMATOLOGY

Since the disease is characterized by polymorphism of the eruption, the diagnosis is not infrequently a surprise in cases in which it is made on the laboratory findings.

Sporotrichosis may conveniently be described as conforming to one of two different clinical types: the disseminated type and the localized, or epidermal type. There is a different pathogenesis in these two clinical types.

In the disseminated type, the infection may spread from its original localization in a gummatous focus to any part of the body, dissemination usually taking place first through the lymphatics and later through the blood stream. Occasionally, however, the infection enters the blood stream directly and dissemination occurs in this manner.

The lymphatic form of dissemination usually starts on an extremity some 20 days after an injury as a red, painful swelling at the site of the inoculation, which grows within two weeks to become a purplish nodule varying in size from 3 to 5 cm. in diameter. This is the sporotrichotic chancre, which soon softens and discharges a sticky or blood-tinged fluid. The ulcer which forms as a result of the rupture of the chancre is superficial and has punched-out margins. The base is dotted with blood-tinged punctate elevations, resembling pyogenic ulcer.

The ulcer remains unchanged for several weeks, finally awakening the suspicion of cancer in the patient's mind. About this time, a few purplish nodules appear along the course of the regional lymphatics. The nodules in this form of ascending lymphangitis rapidly grow to the size of a hazelnut, becoming attached to the skin, and after a few days, soften and form an ulcer which soon becomes covered with a black crust. The ulcer ultimately heals with a scar resembling that of scrofuloderma associated with bridge-formation and keloids.

Latapí recognizes a type of regional lymphangitis occurring on the face of infants. The mother usually gives a history of the child having received an injury to the face, after which a pimple appeared at the site of injury. The nose is most commonly affected, becoming involved in an inflammatory process whose most characteristic feature is the formation of small nodules disposed in ladderlike pattern along the regional lymphatics. The nodules have the appearance of folliculitis. They do not ulcerate. In Costa Rica, this type of sporotrichosis may easily be confused with leishmaniasis.

The epidermal form is characterized by polymorphous lesions and widespread distribution and may resemble such disorders as acne, tuberculosis and epithelioma. The epidermal form represents a hyperergic reaction on the part of the host tissues to the invading fungus

There are acneform, ulcerating, verrucous, erythematous, psoriasiform and follicular varieties of epidermal sporotrichosis, as well as forms resembling dermatitis vegetans and bacterial dermatitis The acneform lesion consists of a group of tiny pustules which characteristically occurs on only one side of the face and discharges a thin serous fluid which quickly dries and forms a dirty looking crust.

Ulcerating epidermal sporotrichosis is marked by the formation of polycyclic, firm, indolent ulcers with punched-out margins, occurring exclusively on the extremities. The ulcers run a chronic course, usually being associated later with regional lymphangitis.

Verrucous epidermal sporotrichosis is important because the diagnosis is difficult to establish except by exclusion. The lesions offer confusion with verrucous tuberculosis, leishmaniasis, dermatitis vegetans, and chromoblastomycosis. There are no clear-cut distinguishing features whereby this form of the disease may be recognized.

The erythematous form consists of several small pustules located in well-defined patches of scaling erythema, resembling patches of bacterial dermatitis. The psoriasiform and follicular varieties are uncommon.

DIAGNOSIS

The mycologic diagnosis of sporotrichosis is easily made by routine laboratory procedures.

The direct microscopic examination of smear preparations of pus obtained from human lesions is invariably negative for Sporotrichum, the reported findings of raylike bodies and other structural abnormalities being too infrequent to be of diagnostic value.

The fungus grows readily on Sabouraud's glucose agar slants at room temperature the fungus showing growth within three to five days. The colonies at first are pearly white, smooth, and without aerial mycelium After 11 days the color turns darker and the surface becomes crateriform or wrinkled.

Microscopically the fungus appears as thin, branching, septate hyphae with short lateral branches bearing clusters of conidia of varying size and shape, depending on the age of the culture.

Animal inoculation is not necessary to establish the diagnosis.

The histologic examination of infected tissue reveals changes characteristic of a chronic nonspecific granuloma. There are also foci of suppuration and, in the papillomatous form, intra-epidermal abscesses. The fungus is present in the tissue and reacts positively to the periodic acid-Schiff technique.

Hypersensitivity in patients with sporotrichosis has been difficult to determine until recently due to the use of unreliable antigens made from the whole fungus. Gonzalez Ochoa and Figueroa have lately prepared an antigen from the polysaccharide fraction of S schenckii, which has proved 100 per cent specific. The test is performed with the intradermal injection of 0.1 cc. of the extract, and readings are made 24 and 48 hours later In positive cases, there is an erythematous halo not less than 3 cm. in diameter and a papule at least 5 mm. above the level of the skin.

In blood-stream dissemination of the infection, the test is strongly positive, occasionally however giving rise to systemic reactions of alarming proportion. Strongly positive reactions are also noted in the localized forms. Such reactions are regarded as indicating great resistance on the part of the host tissues to the fungus.

PROGNOSIS AND TREATMENT

The prognosis as to life is generally good except in cases of the acute disseminated type, in which a fatal outcome usually supervenes. In the localized type, delay in establishing the diagnosis may result in cosmetic disfigurement and limitation of motion of the arm or leg, as happened in a recent patient of mine. This patient had not received treatment and when he came under my care, there was extensive scarring of the right arm and forearm, fixation of the elbow making it impossible for him to extend his arm, the arm being fixed in a flexed position.

The use of potassium iodide is curative in practically 100 per cent of cases. Treatment is begun with 0.25 gm. daily in order to test the patient s tolerance to the drug If signs of intolerance

appear intradermal desensitization with diluted Sporotrichum extract is carried out by gradual increases of dosage. When desensitization is obtained, the dose of potassium iodide may be rapidly stepped up to as much as 4 or 6 gm. daily Treatment should be continued at this level for at least one month after complete healing of the lesion or lesions, to prevent relapse.

Surgical intervention in combination with physiotherapy is occasionally required in cases associated with disfigurement or deformities.

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11

Chromoblastomycosis

By
Alfonso Trejos

Definition. Chromoblastomycosis is a polymorphous granulomatous disease limited to the skin, which is caused by various species of dematiaceous fungi having as a common feature their appearance in tissue as round, thick walled, yellowish-brown, septate elements measuring approximately 10 microns in diameter The most common synonyms for the disorder are verrucous dermatitis and chromomycosis.

Geographic distribution. The disease has been reported from all parts of the world except continental Asia, being most frequently encountered in tropical and subtropical regions.

Age, sex, and occupation incidence. A total of around 400 cases have been reported in the literature, 78 per cent of which were reported from the following five countries: Brazil 32 per cent, Costa Rica 15 per cent, Cuba 11 per cent, Venezuela 11 per cent, and Australia 9 per cent.

The rural population is affected almost exclusively due most likely to the saprophytic existence of the etiologic agents on grass and plants. The disease may occur at any age, but the majority of cases are found in adults.

The port of entry of the fungus is always a break in the continuity of the skin occasioned by injuries sustained by agricultural workers. For this reason, the highest incidence is found in males, the ratio of females to males being 1:12. Nevertheless, this ratio is not correct for all countries, since there is no report of the disease occurring in women in Australia and Cuba, there was only one woman in 58 cases studied in Costa Rica, while in Venezuela, among 34 patients reported by Campins and Scharyj, there were 15 women.

Localization of lesions. The infection is located most frequently on the distal third of the legs and less commonly on the arms, head, neck, and trunk. This order of predilection does not hold true for all countries, since Powell in Australia found the primary lesion on the legs in only 3 of his 29 patients. It is therefore evident that any part of the skin may be affected, particularly exposed parts of the body I have not been able to find a report of mucosal lesions.

Symptomatology The primary lesion is a small papule which appears a few days or weeks following the entrance of the fungus in the skin. Subjective symptoms are generally absent. The papule slowly extends eccentrically to form a vegetating patch which reaches a size of 1 or 2 cm. within two or three years. Ten years are usually required to attain a size of 10 cm. in diameter after which it often fuses with other lesions which have appeared through the years to form a large, vegetating sheath covering a large part of the leg Dissemination of the infection usually takes place through the superficial lymphatic vessels and occasionally through the deep lymphatic vessels.

In advanced instances of the disease, the lesions on the legs often appear as tumorlike masses which may become pedunculated. On the arms, tumor-formation does not occur instead, the lesions are usually dry hyperkeratotic patches with central clearing.

Romero and I believe that there are two clinical types of the disease the dry verrucous and the moist, vegetating type. The frequent occurrence of secondary infection in lesions of the leg probably accounts for the moist, vegetating character of the lesions in this region. The great number and variety of bacteria in these secondarily infected lesions gives rise to their characteristic goatlike odor

Some lesions ulcerate as a result of secondary infection, maceration of the vegetations, or dissemination of the infection through the deep lymphatics. Dissemination of this kind is responsible for clinical pictures resembling sporotrichosis, with ulceration and suppuration of the draining lymph nodes.

Fibrosis sometimes develops in the deeper tissues and produces elephantiasis, probably as a result of repeated attacks of erysipelas.

Spontaneous involution of lesions is unknown to me, although it is not unusual to find central scarring in extensive lesions.

The disease should be differentiated from tuberculosis verrucosa cutis, verrucous leishmaniasis, sporotrichosis, late syphilis, dermatitis vegetans, and yaws. The great similarity in appear ance of the cutaneous lesions of these various diseases often renders the clinical diagnosis difficult, so that confirmation of the diagnosis should be obtained by the mycologic examination.

Histopathology In histologic sections, the appearance of chromoblastomycosis is very much like that of other fungous granulomas, with particular involvement of the epidermis and the papillary portion of the dermis. The epidermis constantly shows considerable hyperkeratosis and acanthosis, resulting in many sec tions in the formation of pseudo-epitheliomatous hyperplasia. Both the horny and the prickle-cell layers may show an infiltrate containing micro-abscesses consisting mainly of polymorphonuclear leukocytes.

In the dermis, there are papillary hypertrophy and a diffuse or focal infiltration composed of a large variety of cells such as poly morphonuclear leukocytes, eosinophils, lymphocytes, plasma cells, histiocytes, Langhans and foreign-body giant cells. Occasionally Russell bodies are also present. Rarely as in the case reported by Carrion and Silva, the infiltrate has a tuberculoid structure.

There is also extensive fibrous thickening of the dermis, par ticularly marked in sections of advanced lesions However fresh lesions also show a tendency to become walled-off by fibrous tissue

The small blood vessels are dilated, and there is an inflammatory infiltrate around the walls of the vessels, with occasional for mation of focal areas of necrosis. There is also new blood vessel formation.

The etiologic agents appear as single, fumagoid elements (sclerotic cells) in the micro-abscesses, in the tissue between the poly morphonuclear leukocytes, and in giant cells. Fumagoid forms are sometimes found in the horny layer where they bear hyphae.

Mycology The etiologic agents of chromoblastomycosis belong to the family Dematiaceae of the Fungi Imperfecti. The manner of sexual reproduction of these fungi is not known. Al-

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though Ajello and Runyon as well as Karrer and Conant have described some cleistothecíae, it has not been possible to demonstrate an ascus with ascospores in its interior

There is no unanimity of opinion regarding the generic position of the various species causing chromoblastomycosis. My criterion for determining the genera has been adopted by Carrion. According to this formulation, the various etiologic agents can not be compressed into a single genus· rather they may be included in three genera, i.e., Cladosporium, Fonsecaea, and Phialophora.

The most widely distributed and most frequently encountered species is Fonsecaea pedrosoi. Next in order of frequency is Cladosporium carrionii, which has been isolated in Venezuela, South Africa, and Australia. A smaller number of cases have been caused by Phialophora verrucosa and Fonsecaea compacta. Fonsecaea dermatitidis and Phialophora jeanselmei were each found in but one patient with the disease the latter species more often producing black-grain mycetomas.

The classification of these different species can only be made by the microscopic examination of cultures, since all species have the same appearance in parasitized tissue and produce the same clinical picture. Neither has the gross appearance of the culture any taxonomic value.

Each strain possesses characteristic conidiophores by which it is possible to classify these fungi in genera and species Slide cultures should be made in order to determine exactly the structure of the conidiophore and the arrangement of the conidia. The use of slide cultures is necessary because of the extreme fragility of these elements. The fungi grow best on corn meal agar

The biochemical properties of the dematiaceous fungi have neither specific nor generic value, but the proteolytic activity of species of the genus Cladosporium makes possible a division of these species and pathogenic, nonproteolytic species. Among these are Cladosporium carrionii, an etiologic agent of chromoblastomycosis, and Cladosporium trichoides, a causative agent of brain abscess recently isolated in the United States.

Laboratory methods of diagnosis. Serologic methods of detecting complement fixing antibodies and skin tests to determine hypersensitivity have little practical value in chromoblastomycosis. The direct microscopic examination of properly selected material

readily shows fumagoid forms of the fungus. Material is best obtained from areas which appear caseous under glass pressure, the material in these areas consisting mainly of intrapapillary accumulations of keratinized epithelial cells. This material should be examined microscopically after placing it on a slide and covering it with a cover slip No potassium hydroxide, lactophenol, or other commonly used substance should be added to the fungus in such material. I have never had difficulty in finding the fungus in such material. When, however it is impossible to obtain such material, crusts from verrucous lesions should be mounted on slides in a drop of 10 per cent potassium hydroxide solution.

The examination of tissue obtained by biopsy is usually not necessary in most cases because of the ease with which the fungus can be demonstrated by direct microscopic examination. Cultivation of the fungus is used to determine the species of the fungus and to secure sufficient material for further study at a later time.

Treatment. When the disease is diagnosed in its early stage which is generally within the first three years of its evolution, the treatment of choice is surgical excision. The resection should be made well beyond the edge of the lesion and should extend down to the fascia, recurrences are common if this injunction is not heeded. The destruction of large lesions by electrocoagulation or superficial excision is attended by dire consequences, among which are ulcers, recurrences in situ, and lymphatic dissemination.

Bonilla recently introduced the use of calciferol in the treatment of chromoblastomycosis, his preliminary report of results obtained in three patients being highly encouraging Since this report was written, an additional seven patients have responded satisfactorily to this therapy Treatment consists of the oral administration of 600 000 units of calciferol weekly Activation of the lesions as shown by the occurrence of frequent hemorrhages is usually observed during the first few weeks of treatment with calciferol, after which the lesions flatten out.

The administration of calciferol is continued until the lesions have disappeared and do not yield fungi. Several patients were given 3 gm. of potassium iodide by mouth daily *in addition to the* weekly dose of calciferol, the combination resulting in more rapid evolution of the lesions.

No toxic effects were observed.

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12

Histoplasmosis

By

Dagoberto O Pierini

Histoplasmosis or reticuloendothelial cytomycosis was considered a rare disease until a decade ago when reports of a large number of cases began appearing in the world literature. Today statistics indicate that histoplasmosis is one of the most widely distributed systemic mycoses.

The principal factor contributing to the apparently great increase of reported cases is the awareness of physicians of the protean symptomatology of the disease, together with the development of better staining and cultural methods for the detection of the fungus.

Histoplasma capsulatum is a parasite of the reticuloendothelial system, producing tuberculoid granulomas and focal areas of tissue necrosis. In histologic sections, the fungus shows as a round or oval body in the large mononuclear cells, its size varying between 1 and 5 microns in diameter The clear halo surrounding the fungus in tissue stained with hematoxylin and eosin appears as a bright red cell membrane when it is stained with the periodic acid-Schiff reaction. The halo may also be seen under the electron microscope and is apparently an artefact produced by the cytoplasm shrinking away from the cell membrane.

The cultures developing on Sabouraud's glucose agar, blood agar honey agar and beef infusion glucose broth are white and cottony with elevated borders and shiny central buttons.

Microscopic examination of these colonies shows the mycelium to be composed of delicately branching, septate hyphae bearing small round spores on short lateral branches of the hyphae. Spore formation is well seen in cultures grown on Sabouraud's glucose

agar at room temperature, while it is only occasionally found in cultures grown on medium incubated at 37 C.

Darling believed at first that histoplasmosis was indigenous to tropical and subtropical areas, coming to this conclusion from his study of patients in the Canal Zone Experience has shown, however that this is not so, immunologic surveys indicating that the disease assumes endemic proportions in the lower Mississippi valley of the United States and in the environs of Buenos Aires. The next highest incidence is found in Brazil and a much lower incidence in Uruguay Ecuador and Chile.

In the United States and Argentina, the endemic occurrence of the disease in certain geographic areas helps to distinguish it from other disorders of a similar appearance. The disease to be distinguished from histoplasmosis in the United States is tuberculosis, while in Argentina it is the mucosal form of South American blastomycosis, a disorder occurring with great frequency in northern Argentina and the adjacent provinces of Brazil.

North American authors ascribe great importance to immunologic reactions in marking off endemic zones, especially if the outcome of these reactions coincides with the radiographic appearance of the lungs in tuberculin-negative subjects.

The disease occurs with greatest frequency in infancy and middle age. Male and female infants are affected with equal frequency but in adults, the predominance of male patients is great. Formerly believed to be a disease of rural districts it is now recognized as a disease affecting residents of urban and rural districts with equal frequency

Although commonly appearing in sporadic form recent reports indicate that histoplasmosis may occur epidemically with pulmonary manifestations of cavitation, empyema, consolidation and pleuritis. These extensive and severe pathologic changes contrast with the relatively mild nature of the clinical symptoms which disappear in two or three weeks. The pulmonary lesions, on the other hand, sometimes require a long time to disappear and often leave residual miliary areas of calcification

The manner in which man becomes infected is not well established. A putative source of infection is the soil, where the parasite completes a developmental cycle as a saprophyte of decaying

vegetable matter From here the fungus is possibly transmitted to man by dogs or wild rodents, a concept which is now out of favor Milk is blamed by some as a source of infection. Transmission of the infection from man to man has not been reported.

The ports of entry differ in infants and adults, the predominance of gastrointestinal symptoms in the former suggesting that the fungus gains entrance through the intestinal mucosa, while the primary involvement of the respiratory tract in adults points to an invasion of the oral and nasopharyngeal mucosae. Primary cutaneous infection is rare.

The high incidence of respiratory tract involvement in adults tends to support the concept maintained in the United States that the infection is air-borne and enters the respiratory tract of individuals exposed to various dusts, such as that from chicken or pigeon manure or from the soil.

The course of the disorder is different in infants than in adults. A division of the infantile and adult forms into mucocutaneous and systemic types is purely didactic, since the disorder often begins with manifestations of the former type and ends with the systemic type.

The clinical picture of infantile histoplasmosis is so lacking in characteristic signs and symptoms that the diagnosis is usually not made before autopsy

The symptoms are those of an infectious disease. The child begins to lose weight and appetite and grows pale. He becomes highly irritable. Digestive disturbances make their appearance and gradually increase in severity There is a progressive enlargement of the liver and spleen and mild to moderate involvement of the lungs. Associated findings of anemia and leukocytosis (or leukopenia) and thrombocytopenia are present.

The radiographic examination of the lungs generally reveals small shadows corresponding to the slightly enlarged hilar lymph *nodes and some peribronchial thickening. Although* these findings are similar to those of tuberculosis, the diagnosis of tuberculosis may be excluded by the negative tuberculin reaction and by noting the birthplace of the child.

Lesions of the skin and mucous membranes in these little patients are rare. The occurrence of vesicles, pustules, ulcerations,

and purpura a few days before exitus has been noted in a few cases.

The diagnosis is definitely established by the direct examination of material obtained from the sternal marrow The finding of the fungus serves to distinguish histoplasmosis from such similar appearing diseases as tuberculosis malaria, splenic anemia, Gaucher's disease, visceral leishmaniasis, and other febrile disorders.

Although the course of the disease in infants is usually steadily downward to a fatal termination, there are reports on record of therapeutic and spontaneous cure.

The localization of adult histoplasmosis in the skin and mucous membranes is of great importance to the dermatologist. For purposes of discussion, the disorder in adults may be divided into circumscribed and disseminated forms.

The circumscribed forms are characterized by the presence of lesions of the oral, nasal, and pharyngeal mucosae and adjacent skin, by the absence of demonstrable visceral involvement, by the benign course of the disease, and by the favorable response to the sulfonamides.

The primary symptoms are varied. There may be areas of ulcerating gingivitis resulting from the extraction of teeth, from rhinitis, or hoarseness, the latter symptom often bringing the patient to the physician because of the fear of cancer

Any of the following lesions, either singly or in combination, may be found in adult patients with circumscribed histoplasmosis:

1. Irregular shaped, clean looking, fairly deep ulcers with red margins and a granulomatous base which is dotted with whitish spots, without induration or noticeable inflammatory reaction. The ulcers result from softening of the gummatous nodules which often greatly simulate those of South American blastomycosis.

2. Ulcerative lesions developing singly or in corymbose fashion.

3. Nodules with a surface which is either smooth and shiny or rough and papillomatous. They usually arise in areas not exposed to constant irritation, such as the larynx.

4. Cheilitis, particularly of the upper lip associated with diffuse swelling and induration of the lip

5. Frosted appearing red nasal mucosa, seeded with pinhead sized white dots, a frequent forerunner of involvement of the sep-

tum leading to its ultimate destruction. The resultant disfiguration is reminiscent of the tapirlike appearance of some patients with South American blastomycosis or American mucocutaneous leishmaniasis although to a milder degree.

The nodular lesions generally arise in the larynx, epiglottis, and occasionally on the vocal cords, while the ulcerations most commonly develop either in the gums around the last molar tooth or on the dorsum of the tongue, where the destructive process leads to a rhomboidal ulceration that closely resembles a tuberculous ulcer.

An interesting feature of this form of histoplasmosis is the loss of almost all of the teeth, patients usually giving a history of having lost their teeth over a period of months or years. It is possible that the teeth participate in the general disorder before the disease shows itself elsewhere, since several authors claim that they have been able to prevent the teeth from falling out by instituting early treatment with the sulfonamides in patients with ulcerations around the molars.

The regional lymph nodes are usually greatly enlarged.

Except for a serious loss of weight, there are generally few signs of visceral involvement in this form of histoplasmosis. At times, however, there are associated symptoms of renal and adrenal insufficiency.

All reported cases of histoplasmosis up to 10 years ago were instances of disseminated histoplasmosis with an invariable fatal termination.

Disseminated histoplasmosis may manifest itself from the onset as such or as circumscribed histoplasmosis which suddenly becomes disseminated. A third possibility results from the sudden activation of latent foci in the lungs, appendix, prostrate, or other viscera.

The associated constitutional symptoms are common to any febrile disorder. The specific symptoms depend on the particular tissue or organ affected. In the order of frequency of involvement, they are

1. *The lymph nodes.* There is enlargement of all the lymph nodes, particularly the cervical, mediastinal, and mesenteric.

2. *The liver and spleen.* Enlargement of these viscera is rarely absent.

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5. Frosted appearing red nasal mucosa, seeded with pinhead sized white dots, a frequent forerunner of involvement of the sep-

7 *The nervous system and kidneys* only infrequently participate in the general disorder. Blood changes, if present, are not specific.

The histologic examination shows a chronic granulomatous infiltrate and several foci of necrosis which often increase in size and bring about the total destruction of the affected organ. Caseation, however, is not found.

Many large histiocytes are seen engorged with parasites and surrounded by epithelioid and giant cells. Their number depends on the immunologic situation of the host, being most abundant in benign forms of the disease. The appearance of the fungus in the tissues was previously described.

The frequent concomitant occurrence of tuberculosis or the lymphoblastomatous-Hodgkin's disease group of disorders appears more than fortuitous. Current research has failed to show whether tuberculosis predisposes to the development of mycotic disease, or if the tuberculous infection becomes disseminated as a result of the breakdown of the natural defenses, this breakdown allowing dormant foci of infections to become activated. Autopsy statistics indicate that histoplasmosis and tuberculosis are found coexistent in most cases.

On the other hand, the authenticity of reported cases of coexistent Hodgkin's disease or leukemia is not well established, because the enlargement of the lymph nodes and the increase in number of circulating leukocytes, with the absence of immature forms, are both encountered in patients with histoplasmosis.

The question of whether histoplasmosis is responsible for the calcification found on radiographic examination of tuberculin-negative subjects is of great importance to Public Health officers. It will be recalled that South American blastomycosis and coccidioidomycosis can also produce calcification of the hilar lymph nodes.

The diagnosis of histoplasmosis may be extremely difficult in the absence of characteristic symptoms.

To establish the diagnosis, suspected material from lesions of the mouth, larynx, or skin, as well as from enlarged lymph nodes or the spleen should be stained for histologic study and smeared

and stained for demonstration of the fungus. It is not always possible to demonstrate the organism in material obtained in this manner due to the small number of parasites in the lesions of circumscribed histoplasmosis or to the improper selection of material. Suspected material should be placed in liquid media fortified with penicillin and streptomycin to avoid bacterial contamination. Animal inoculation has not proved consistently successful in my experience.

The fungus can also be demonstrated in the sputum, stomach washings, pleural effusion, and sternal marrow In adults, the marrow generally fails to yield the organism, in contrast with the situation in infants in whom positive yields are almost always obtained.

The serologic tests for the detection of precipitating and complement fixing antibodies in the sera of patients with this disease have recently gained wider usage due to the availability of commercial antigens. However the possible occurrence of cross reactions with antigens prepared from Blastomyces dermatitidis and Coccidioidis immitis should be kept in mind.

Intradermal testing with histoplasmin is of little diagnostic value. A positive reaction in a person living in an endemic zone simply indicates that he once had the disease, while a negative response in patients with generalized histoplasmosis is an indication of an anergic situation similar to that in the terminal phase of tuberculosis and coccidioidomycosis.

TREATMENT

The sulfonamides and ethyl vanillate have proved the most effective of all the many therapeutic agents used in histoplasmosis.

It is difficult to explain the lack of response of North American patients to the sulfonamides in contrast with the favorable response of South Americans.

This discrepancy may possibly be attributed to the circumstance that treatment in South America has been almost exclusively limited to patients with circumscribed histoplasmosis. However as occurred in a recent patient of mine, the sulfonamides have been equally effective in disseminated histoplasmosis.

Treatment with the sulfonamides should be started as early as possible in the course of the disease, before pathologic visceral changes have occurred. Large doses should be given and maintained for a long time.

The combination of sulfadiazine, sulfamerazine, and sulfamethazine has proved most effective and is the least toxic.

Ethyl vanillate has been particularly effective in North American cases of infantile histoplasmosis, although its effectiveness is only slightly superior to that of the sulfonamides. The recommended dose is 1.5 mg. per kilogram of body weight daily divided into four or five doses. The slight margin of safety between effective and toxic blood levels renders the use of this drug hazardous.

Mucosal lesions often respond favorably to x-ray therapy or surgical extirpation.

The reported favorable results with stilbamidine have not been confirmed in South America, and the high degree of toxicity of this drug renders its use inadvisable.

The cryptospores and vacuoles may appear as peripherally situated minute buds as they emerge from the mother cell. At these times, they may resemble certain types of the tissue forms of C immitis.

The direct examination under subdued light from the microscope condenser of pus obtained from a large facial lesion in a patient observed in Bolivia revealed both single and multiple budding, thick walled yeastlike cells of 8 to 50 microns in diameter some of which resembled the thick walled, round chlamydospores in late growths of H. capsulatum from Sabouraud's glucose agar at room temperature.

Furtado and his associates cite the studies of Aroeira Neves and Bogliolo to show that the causative fungus of this disease might better be named Aleurisma brasiliensis because the microscopic examination of fully developed adult colonies grown on corn meal agar reveals the characteristic aleurospores. These structures differ from the true conidia in not becoming detached from the mycelium by dehiscence but instead remaining attached to the dead and empty hyphae.

Tissue examination is not revealing, because P brasiliensis often produces tissue changes similar to those caused by C. immitis and B dermatitidis. Neotropical blastomycoid granulomatosis has a lesser tendency to suppurate and a greater tendency to form fibrosis than has its counterpart in the North American countries.

The fungus may be identified within the giant cells by the periodic acid-Schiff technique or better still by ammoniacal silver impregnations recommended by Bogliolo.

Immunology A standard serologic technique for the detection of complement fixing antibodies has not yet been worked out. Likewise, the detection of hypersensitivity by means of the intradermal injection of antigen has not been uniformly possible because of the lack of a standard antigen.

Treatment. Although encouraged at first by the results obtained with the sulfonamides, Negroni, and Furtado and his associates have lately been disappointed in this form of therapy At the best, the sulfonamides probably exert a temporary suppressive effect only

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The growths obtained by Fonseca and Siqueira-Carneiro failed to produce lesions when inoculated into animals and, in the case of Siqueira-Carneiro were not sufficiently described to be of taxonomic value.

I believe, therefore, that we should continue using the term by which the fungus was originally designated, i.e., Glenosporella loboi, understanding by this designation the form assumed by the fungus in human tissue. In view of our scant knowledge of this fungus, it seems premature to try to include it in the synonymy of one of the causative agents of other blastomycoses.

Treatment. Surgical excision of well-demarcated lesions has given good results. In extensive lesions of long duration, it is impossible to excise all of them, and the surgeon should restrict himself to removal of lesions which are causing discomfort to the patient. This procedure will prevent new lesions from appearing in these areas for at least a few years.

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clude a diagnosis of blastomycosis. The periodic acid-Schiff reaction is valuable in this connection. This technique colors the thick, highly refractile wall of the organism magenta, and in tissues stained with this technique, the fungus stands out clearly against a bluish background, especially if the examination is made under reduced light.

Mycology B dermatitidis grows in the tissues as a single or budding, yeastlike cell with a thick membrane, measuring from 8 to 16 microns in diameter The size of the fungus should be accurately determined with an eyepiece micrometer in order to exclude fungi like Cryptococcus neoformans, which possess a similar yeast phase in tissue.

B. dermatitidis differs from Cryptococcus neoformans in that cultures of the latter remain yeastlike regardless of the temperature at which they are grown. Difficulty may be encountered in separating cultures of B dermatitidis from those of P braziliensis, because both fungi develop as a yeastlike organism at 37 C. and as a filamentous mold at room temperature, so that a microscopic examination is necessary to distinguish between the two organisms. B dermatitidis usually multiplies by single budding, whereas P braziliensis produces numerous buds along the outside of the cell wall.

Immunology The degree of hypersensitivity as measured by the reaction of the host to the intracutaneous injection of fungus-vaccine or blastomycin and to the complement fixation test varies during the course of the infection. Both tests should always be employed as prognostic and therapeutic guide posts, for when used singly especially as diagnostic aids, they may be misleading. A positive reaction to either of the tests indicates that the patient has blastomycosis. A negative reaction, however does not imply the absence of infection, for in this instance either the antigen used to fix the antibodies is of insufficient combining power or the patient has failed to acquire specific immunity and therefore does not respond to the intracutaneous test. The prognosis in this instance is poor

Treatment. Early excision of blastomycoid cutaneous lesions with the knife or electrocoagulation is the best treatment. If the process is already too extensive for this procedure, the judicious

use of x-rays in conjunction with the oral administration of Lugol's solution and the topical application of streptomycin compresses will frequently reduce the secondary bacterial infection to a point where the use of surgical diathermy will bring about a cure.

Although stilbamidine has proved successful in arresting a number of instances of the disorder the occurrence of hepatitis, nephritis, fifth nerve damage, and frequent relapses during and after the treatment has shown that the drug is by no means harmless. The search for less toxic agents is being pursued.

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RHINOSPORIDIOSIS

Symptomatology. A typical instance of the infection was observed in Bolivia. The patient showed a large, purplish-red vegetating, polypoid mass extending down from the nose and over the upper lip. On close inspection, tiny white spots were detected scattered throughout the papillomatous growth which bled easily at the slightest touch. Two small, wartylike granulomatous lesions were present on the left cheek. There was no associated pain.

The disorder should principally be distinguished from pyogenic granuloma, epithelioma, hypertrophic rhinitis, conjunctivitis, neotropical blastomycoid granulomatosis, and cryptococcosis. In a patient suffering from neotropical blastomycoid granulomatosis observed in Bolivia, a large polypoid mass extended up through the nasopharynx from its seat of origin in the mouth, to fill the entire nose. The appearance of this growth was that of a sessile polyp of rhinosporidiosis differing from it, however, by the absence of white spots.

Mycology. Since no media are available for culturing the causative agent of rhinosporidiosis, scrapings of suspected material should be examined directly in a drop of water under a cover slip. Biopsy material should be stained with the periodic

acid Schiff technique. The typical spore-filled sporangia, identified clinically as minute white spots can be found in both fresh smears and tissue sections. There are about 16,000 spores in a mature sporangium, practically all of which are ultimately discharged through an opening in the sporangial wall, similar to the liberation of endospores of Coccidioides immitis from their spherule.

Treatment. Although the smaller lesions of rhinosporidiosis do not provoke discomfort and may even undergo spontaneous involution if left alone, it is nevertheless best to remove them as soon as possible with the knife, because they generally continue to grow in size until they finally cause obstruction in the larynx. Great care should be taken in excising the polyps, in order not to rupture the sporangia and cause dissemination of the organism through the body It is good practice to cauterize the base of the polyp after its removal.

CRYPTOCOCCOSIS

Symptomatology The skin occasionally serves as a port of entry for the organism, in which event isolated lesions such as abscesses and ulcers of the skin and subcutaneous tissues may occur the fungus being readily obtained by aspiration or swabbing. A patient under observation showed numerous, reddish-brown, acneform lesions with several small ulcers distributed over the face, neck, and body which appeared in the terminal phase of the infection.

Mycology Suspected material which is free from pus and tissue particles should be examined unstained directly under reduced light or after mixing with a drop of dilute India ink. The capsule will then appear as a clear halo surrounding the cellular membrane. If, on the other hand, there is an admixture of pus and tissue cells, it is better to stain with the periodic acid Schiff technique. As a consequence of the action of periodic acid, the cellular membrane begins to break down.

The wide capsule of C. neoformans is composed of a polysaccharide which renders it resistant to the action of acids and alkalies of different composition. Negroni and Lanata attempted to reduce the size of the capsule by exposing the fungus to such

various substances as pancreatic amylase, hyaluronidase, and acid and alkaline solutions but they failed to observe more than a slight effect on the capsular formation.

The presence of such a wide capsule probably serves to inhibit the formation of antibodies and explains the failure to demonstrate agglutinins or precipitins in the sera of infected persons The lack of tissue reaction to the fungus is also due to the wide capsule. Intracutaneous tests made with vaccines and extracts of the fungus have likewise proved unsuccessful.

C. neoformans in cultures assumes yeastlike forms regardless of the temperature at which it grows The capsule does not appear on primary cultivation, several growths being required for it to develop In its nonbudding phase the fungus may be mistaken for C. immitis and B dermatitidis. The Glenosporella like organism described by Lobo shows only single budding, and that in tissue sections only

Treatment. The sulfonamides have proved effective in some patients, while in others they have failed to stop the progress of the infection The antibiotics have proved ineffective. Cutaneous lesions are best excised and the operative wound exposed to the x rays.

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GEOTRICHOSIS

The causative fungus of this infrequent mycosis is Geotrichum candidum. Our only concern with it is that it sometimes produces oral lesions consisting of white patches which greatly resemble those of thrush and that its appearance on microscopic examination bears close resemblance to that of B dermatitidis.

A confusion of the spherical forms of G candidum with the budding forms of B dermatitidis may be avoided by cultivating Geotrichum on Sabouraud's glucose agar plates at room temperature. The resulting cultures are soft and yeastlike and continue to form arthrospores by segmentation of the hyphae, in con

trast with the cultures of B. dermatitidis which often show segmentation of the hyphae on primary cultivation but soon become filamentous and produce conidia.

The use of alkaline mouth washes and gentian violet in oral infections due to Geotrichum has been recommended.

16

Mucocutaneous Candidiasis (Moniliasis)

By
Frederick R. Schmidt

THE CLINICAL and mycologic features of classic Candida infections of the skin, nails and mucous membranes are usually recognized and described. A few unusual features, however merit attention.

The nails are most commonly infected as a consequence of Candida infection of the paronychial tissues. Occasionally however this is not so. Negroni described several instances of patients in whom the infection first involved the free border of the nail, whence it spread to the nail bed.

A man recently entered the hospital complaining of diarrhea and extreme weakness The routine examination disclosed a severe degree of macerated, vesiculobullous dermatitis of both hands. C. albicans, although abundantly present in the stools, was not found in material obtained from the hands. No evidence of the presence of filamentous dermatophytes was found on the hands or feet. It was therefore concluded that the dermatitis was an expression of the intestinal activity of the fungus i.e., an "id." With improvement in the man s condition, the dermatitis is slowly undergoing involution.

The occurrence of miliaria associated with the presence of C. albicans or related species in the stools and cutaneous lesions has been reported. Vesiculopustular dermatitis of the vagina, associated with Candida infection is common in diabetes and pregnancy It is an expected finding in pregnancy when one recalls that approximately 18 per cent of normal pregnant women at term yield C. albicans in the vaginal sec ions.

A two-year-old girl recently observed in Costa Rica showed unsightly dirty yellow granulations with multiple horn formations on the face and scalp discrete papules on the arms and legs, and involvement of several nails with paronychia. The laboratory reported finding C albicans in the stools, skin, and nails on direct examination and in cultures. Dr Stephen Rothman repeatedly demonstrated a similar-appearing case in a boy before the Chicago Dermatological Society as monilial granuloma. C. albicans is frequently a secondary invader in tissues primarily infected by other types of fungi. This apparently occurred in the little Costa Rican patient in whom direct examination of material from the skin lesions and nails showed forms belonging to the group of dematiaceous fungi.

Acrodermatitis enteropathica is a syndrome embracing lesions of the skin and nails, loss of hair and diarrhea, occurring mainly in infants between the ages of 3 weeks and 18 months. In contrast with Candida granuloma, however the stools do not yield the fungus, while abundant mycelial elements can be found in the scrapings obtained from the skin lesions. In acrodermatitis enteropathica, therefore, a still unknown intestinal agent is apparently responsible for favoring the localization of the fungus. Treatment with diodoquin is usually effective.

The appearance of C. albicans in scrapings from the skin, nails, and mucous membranes, as well as in cultures, is too well known to merit description Such related species as C. krusei, C. tropicalis, C. stellatoidea, and C. guillermondi show variations from the appearance of C albicans on direct examination, in cultures, and in the fermentation of carbohydrates. The various species are mainly characterized by differences in the structure and arrangement of pseudomycelium, chlamydospores, and blastospores.

The few valid species of the genus Candida of interest to the dermatologist can best be grown on a starvation medium such as yellow corn meal agar or the soil-extract agar medium described by Bakerspigel.

The excellent results obtained with the topical application and oral administration of Mycostatin (obtainable in ointment or capsules of 500,000 units) in patients with superficial moniliasis of

the skin and mucous membranes completely overshadow those following the use of older remedies

The increase during recent years in the number of intestinal Candida infections has been attributed by many to the universal use of the antibiotics. Considerable doubt has recently been cast on this contention by Robinson, who showed that the normal intestinal flora contains C. albicans in 16 per cent of normal persons, and that the incidence of the fungus is not influenced by the use of penicillin or the broad-spectrum antibiotics. Many clinicians will nevertheless hesitate to accept Robinson's interpretations of his in vitro tests since there is a good deal of clinical evidence to the contrary.

An effective remedy against intestinal moniliasis has recently been introduced by Neuhauser. This consists of saturated complexes of an acid adsorbing resin and certain fatty acids, particularly caprylic acid and its nearby homologues, and undecylenic acid. In none of her patients were any toxic reactions due to the use of this therapeutic agent observed. The successful treatment of the intestinal infection may lead to the disappearance of any associated cutaneous manifestations due to C. albicans.

An apparently effective remedy against intertriginous moniliasis has recently been recommended by Franks, Taschdjian, and Thorpe. It consists of an insoluble form of Candidicin and is used in one per cent polyethylene glycol.

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17

Concerning the Superficial Mycoses

By

Frederick R. Schmidt

Keratolysis exfoliativa. This disorder is manifested by a scaling condition of the hands and feet, most probably caused by either T rubrum or the mosaic fungus the former having been isolated in 20 per cent of reported cases The mosaic fungus was formerly regarded either as an attenuated form of Trichophyton or Epidermophyton or as an extracellular deposit of fungi or cholesterol.

Goetz recently interpreted his experiments as indicating that mosaic fungi represent fatty substances formed during the oxidation of fatty material in the normal epidermis. He explains the observation of Dowding that the mosaic fungus is usually found at a higher level than other mycelium in cover slip preparations by the results of his experiments, which show that the oxidation of fatty substances takes place exactly at this level in the epidermis.

Treatment consists in the elimination of any existent fungous reservoir between the toes or in the groin, the use of a few fractional x-ray treatments, and the local application of 2 per cent alcoholic solution of salicylic acid. It is good practice to have patients avoid the use of strongly alkaline soaps and detergents

Tinea versicolor or tinea nigra. This disorder should not be confused with tinea nigra palmaris, a strictly tropical fungous disorder of the palms. The basis for the confusion lies in the color of the lesions the pigmented spots in typical tinea versicolor being brown and black in atypical tinea versicolor The lesions of tinea versicolor show yellowish-brown fluorescence when exposed to Wood's light.

Tinea versicolor and other superficial mycoses are often associated with depigmentations of the face neck, and arms, being

especially common and noticeable in tropical countries where the grayish, slightly scaly spots of varying size and figure are of no little concern to the women of color in those lands. Popularly known as sun children, they stand out prominently not only in darker skinned persons but also in those with light complexions when exposed to the tropical sun. Children living in hot, humid climates are especially affected, since they are constantly rubbing off sweat on their faces and thus infecting the skin with fungi and pyogens. The resulting infection produces a slight scale which partially screens the skin from sunlight, leaving a more or less sharply defined whitish or grayish spot surrounded by normally colored skin. If exposure to sunlight is continued, the loss of pigment persists for a distressingly long time after the scale is cast off

On close inspection, many of these spotted achromias appear stippled with minute, skin-colored elevations resembling goose flesh. They are follicular reactions to the actinic ray and serve to distinguish the actinic achromias from those caused by fungi or pyogens.

These white spots differ from those associated with vitiligo in that they have a grayish color and do not have a hyperpigmented border Patients with pinta usually give a history of previous lesions suggestive of the disorder and show lesions distributed over the entire body

Controversy exists over the mode of production of these white spots. It does not seem reasonable to ascribe them exclusively to the screening action of the fungus or the scale that it produces against the short wave ultraviolet rays of the sun, because they are also found in areas protected against sunlight by clothing. I would rather believe that they are due to the inhibition of the oxidative processes concerned in pigment formation, brought on by the partial destruction by sunlight, of the water soluble vitamins, thiamine and riboflavin, in the skin.

Clinical evidence seems to bear out this point. Patients are instructed to apply the ointment of ammoniated mercury U.S.P twice daily to each white spot and to take three capsules of vitamin B daily Tablets of thiamine and riboflavin are added to the vitamin B capsules when the infection has been eradicated

by the use of ammoniated mercury The results obtained by this method are superior to all others in current usage pigmentation usually taking place within a few months

The use of alcoholic preparations of ammidin and ammoidin has proved disappointing in my experience. The inesthetic appearance of the brown ring surrounding the white spots and the occasional occurrence of severe bullous reactions associated with the treatment speak against the use of these compounds in the treatment of the spotted achromias

Erythrasma is caused by Nocardia minutissima and occurs paradoxically more frequently in the temperate regions of the Americas than in the tropics. It differs from tinea cruris by the absence of itching and signs of inflammation, as well as by the absence of satellite lesions around the principal area of infection.

The patches of erythrasma do not fluoresce under Wood's light, in contrast with those of tinea versicolor Intertrigo should also be considered in the differential diagnosis, but in contrast with erythrasma, intertrigo is moist, acutely inflamed, and has ill-defined borders.

Trichomycosis vulgaris. This disorder is caused by Nocardia tenuis and Corynebacterium tenuis. These organisms are found in the yellow variety of the disorder and when associated with pigment producing cocci provoke the red and black types The resultant yellow red, or black concretions surround the hairs of the axillary pubic, and inguinal regions where they are usually situated on the middle one third of the affected hair The infection is frequent among persons living in hot, humid areas and because of the color of the nodules, it causes a good deal of anxiety in its victims The disease may be separated from white and black piedra by microscopic examination. Shaving the infected hairs and then applying a 1 2000 solution of bichloride of mercury is usually sufficient to destroy the parasite.

Piedra. This is a chronic disorder of the hairs of the scalp and bearded regions caused either by Piedraia hortai or Trichosporon beigelii. Piedra is marked by the presence of stony-hard concretions adhering to the hair shaft, the nodules often being so small that they are easier felt than seen. Black piedra is an

exclusively tropical disease, the dark brown or black color and the hardness of the nodules separating it from white piedra. The concretions in both forms of the disease are firmly adherent to the hair They contain the causative organism which is a thick walled mycelial structure that is wider and coarser than that found in trichomycosis vulgaris. The treatment is the same as for trichomycosis vulgaris.

Tinea imbricata or chimbere. The bizarre picture of concentrically arranged rings of scaling papules scattered over the body is so typical that there is little chance of confusion with other disorders The slightly elevated, serpiginous lesions are marked off from the normal skin by slightly elevated, brownish margins. Isolated instances of the disease occur in Guatemala and Mexico while endemic areas exist in Brazil.

The causative fungus is Trichophyton concentricum, which is readily recovered from the scales as branching chains of filaments composed of cuboidal arthrospores of varying size The disease is generally resistant to treatment and often recurs in spite of apparent cure induced by such various applications as the solution of iodine U.S.P., sulfurated salicylic acid, and ointment of salicylic and benzoic acid N.F

Tinea nigra palmaris or keratomycosis nigricans palmaris. This superficial American mycosis is marked by slowly developing blackish or grayish, discrete, round patches most commonly situated on the palms. On close inspection the patches, of which there are usually only one or two on each hand, are seen to consist of minute black dots. The causative fungus is Cladosporium or Dematium werneckii. Direct microscopic examination with reduced light of material from the pigmented lesions placed in 30 per cent potassium hydroxide solution will show olive-colored, branching, septate hyphae.

Tinea albigena or calor de figo. This disorder is caused by Glenospora albiciscans the infection beginning with large dome-shaped vesicles on the palms and soles Itching is intense The vesicles soon break, leaving erosions which rapidly acquire a dry fissured surface. The process generally terminates with depigmentation

The treatment of these two conditions consists in vigorously rubbing the affected areas with a 5 per cent alcoholic solution of salicylic acid to which is added 2 per cent of iodine crystals.

Tinea of the hands and feet. Epidermophyton floccosum, Trichophyton rubrum, and other species of Trichophyton have been isolated from this disease. It may easily be confused with interdigital intertrigo caused by pyogens. The lesions of both fungous and pyogenic origin often serve as ports of entry for infections leading to peripheral vascular disease and phlebitis.

The application of such acidulated solutions as vinegar or boric acid in water to the moist areas in the early stages of the disorder is usually effective, for it not only restores the normal acid mantle of the body but its acidity is also inimical to the further growth of either fungi or bacteria. Later when the lesions show signs of drying up I have had success with swabbing the affected areas with a 10 per cent aqueous solution of silver nitrate containing 5 per cent of alcohol and then exposing them to the sun or to compression with water-cooled ultraviolet radiation for a minute or two

Tinea corporis. Several different fungi have been recovered from the lesions of this disorder among them being T ferrugineum of the faviform group of trichophytons, Epidermophyton floccosum, Microsporum canis, and Microsporum gypseum. The people of Central America call the skin manifestations of this and similar affections, regardless of the cause, carate, which should not be confused with the same word used in Columbia for pinta.

Tinea cruris. This disorder is commonly caused by Epidermophyton floccosum and various species of Trichophyton and occasionally by M. audouini. It appears in the crotch as sharply delineated, scaling, red areas with an elevated border of vesicles and crusts, beyond which there are usually a few satellite lesions. Usually bilateral, it may also be found in the axillae. Itching is generally intense. Such predisposing factors as perspiration, diabetes, irritation from clothing, leukorrhea, and friction from obesity require attention before antifungal treatment is begun. Riders commonly have this infection in the areas that rub against the saddle. A daily cleansing of the affected area with an acidu-

lated detergent in place of soap followed by the application of solution of iodine U S P and a liberal dusting of borated talc is usually effective.

Tinea barbae. Although uncommon in the Americas, its incidence in Puerto Rico and Haiti appears to be on the increase. In those instances in which the causative fungus is M canis, the infected hairs will show a bright green fluorescence under Wood's light, whereas if T violaceum is the cause, the hairs will appear dull white. Farmers having contact with cattle often become infected with T mentagrophytes. This fungus and T rubrum do not fluoresce when exposed to filtered ultraviolet radiation. The use of epilating doses of x-rays is usually curative in tinea barbae.

Tinea capitis. The fungi most commonly isolated from the *inflammatory lesions of tinea capitis in the United States* are M canis, M gypseum, and T rubrum. In Argentina, T violaceum *is the chief offender Tinea capitis infections caused by* T schoenleini of the faviform group of Trichophytons is uncommon, but when it does occur a history of contact with cattle is usually obtainable. Infections caused by M. audouini generally produce low grade, scaly patches showing little tendency to involute spontaneously in contrast with those caused by species of Trichophyton such as T tonsurans.

Species of the endothrix variety of Trichophyton produce the rare clinical form known as black dot ringworm, which manifests itself as ill-defined areas with many infected hairs in the form of black dots imbedded in the epidermis. The hairs do not fluoresce under Wood's light.

In the West Indies, Central and South America, M canis is the commonest cause of tinea capitis in children. Wood's light has provided a means of separating infections due to M canis from those caused by M audouini. Although hairs infected with either of these fungi fluoresce equally under the light, the fluorescence of M canis infections is a paler green than that of M audouini infections. The ability of M canis to fluoresce does not last very long in contrast with M audouini infections, in which the brilliant green color sometimes persists for months. M canis infections should be suspected when the patient gives a history of contact with a cat.

Cat hairs are also infected at times with M gypseum, T mentagrophytes, and T schoenleini, according to Fuentes, Bosch, and Boudet.

The phenomenon of fluorescence exhibited especially by species of Microsporon has been a great aid until lately in the diagnosis and treatment of ringworm of the scalp. Pipkin and others reported a large number of cases of fungous infections of the scalp in the southwestern part of the United States caused by Trichophyton tonsurans of the crateriform group of trichophytons. Adults as well as children seem to be affected. T tonsurans does not show fluorescence and may therefore escape detection by physicians and nurses examining children with Wood's light. The mildness of clinical signs of infection in adults, taken in conjunction with a certain similarity to such disorders as seborrheic dermatitis and lupus erythematosus, makes an accurate estimate of the incidence of the disease in adults impossible.

My records indicate that approximately 84 per cent of M. audouini and canis infections of the scalp in children clear spontaneously in about three months. Until then the child should wear a skull cap and use the ointment of ammoniated mercury U S P in combination with an acidulated soap to prevent spread of the infection, since I believe that the results with ammoniated mer cury ointment compare favorably with those obtained with more modern fungicidal preparations

If examination of the scalp hairs reveals the presence of T sulfureum or one of the faviform group of organisms, or the infections persist for over five months, x ray therapy is indicated. This method of treatment results in about 90 per cent of cures, this should be followed by manual removal of stubs and fragments of hair

Tinea unguium. This infection is most commonly caused by T rubrum and less frequently by Pseudomonas aeruginosa and C. albicans which often turn the nails green. Nail infections caused by Achorion schoenleini are difficult to cure. M gypseum rarely causes nail infections, which is surprising in view of the circumstance that it is essentially a soil inhabiting fungus, par ticipating in nature in the breakdown of keratinous material constituting the chemical basis of such epidermal tissues as horn, hair and feathers.

I believe that the hyperkeratotic element associated with T rubrum infections of the palms and soles accounts to a great extent for the extreme recalcitrance of these infections, the fungus being enclosed in nail substance providing an ideal nutrient which makes it imperative to remove as much of the infected nail as possible before using topical applications. I therefore make it a practice to send persons with ringworm of the nails to a chiropodist with instructions not to return until every fragment of diseased nails has been removed. Solution of iodine U.S.P and ointment of salicyclic acid and benzoic acid N.F are then rubbed vigorously into the affected areas for many months.

If this does not eradicate the infection, surgical avulsion followed by currettage of the nail bed up to but not including the softer growing nail matrix becomes necessary In this way all the infected keratin can be removed.

Kesten, Benham, and Silva recently reported encouraging results with the use of solutions containing lithium bromide and Asterol (Rothman technique) in the treatment of 32 patients with T rubrum infections of the nails two of these patients were cured and 19 showed marked improvement.

Mycotic paronychia. Commonly caused by the staphylococcus and C. albicans, this condition is only occasionally produced by Mucor a fungus that has been isolated from instances of paronychia in fruit handlers.

Monilial infections of the fingernails. This recalcitrant condition sometimes yields to fractional doses of x rays or application of solutions of gentian violet or sodium perborate. I rarely have success with these methods or any other methods until the patient changes his occupation which is usually one in which he constantly has to wet his hands.

Majocchi's trichophytic granuloma. A case observed in Chile brings to mind the possible distinction of this disorder from other similar appearing conditions. The painful, deep, and granulomatous lesions on the legs had been present for four years repeated examinations for fungi and pyogens having been negative. An intracutaneous tests with trichophytin was made, and surprisingly enough the patient responded very actively to the antigen Subsequent examinations for fungi were negative.

Tinea amiantacea or asbestoslike tinea. The scalp in this disorder is partially covered with a whitish, dry substance which on close inspection is seen to consist of asbestoslike laminated scales bound together at the proximal part of the hair, resembling seborrheic dermatitis, psoriasis, and scaling forms of favus. The scalp usually shows very little inflammatory reaction. The disorder is not uncommon in the tropical lowlands where it is chiefly due to sweating and unhygienic living conditions. These factors probably account for the reports of the finding of streptococci in the lesions. The distinction of this disorder from dandruff or eczema is sometimes difficult, especially if inflammation is added to dandruff, and it extends back of the ears. The condition responds readily to the local application of a 5 per cent salicylic or ammoniated mercury ointment.

Otomycosis. As has been repeatedly pointed out in the last few years, the majority of subacute and chronic cases of suspected otomycosis are due to a bacilluslike organism, Pseudomonas aeruginosa, or to a streptococcus, and not to a fungus. In true fungous infections of the external ear canal, microscopic examination of material taken from the ear generally shows Penicillium, Aspergillus, Mucor or Rhizopus, of which the latter two organisms are similar in structure, both possessing fused hyphal terminals called zygospores. Otomycosis should be chiefly separated from bacterial dermatitis, seborrheic dermatitis, contact dermatitis, and irritant dermatitis.

Fungous infections of the external ear canal are sometimes difficult to cure. The ear should be kept dry and as many as possible of the superficial layers of the epidermis removed with a 3 per cent alcoholic solution of salicyclic acid or with hypertonic saline solution. Thorough cleansing and removal of cerumen and other material are essential.

In Ps. aeruginosa infections, cleansing the ear canal with an acidulated detergent and then using Polymyxin B twice daily generally effects a cure. Ointments containing penicillin are not suitable because penicillin allows an overgrowth of gram-negative Pseudomonas.

The reason for the chronicity of fungous infections caused not only by T rubrum but also by other species of Trichophytons is

not clear In addition to the hyperkeratotic element associated with *T rubrum infections of the palms, soles and between the toes* previously mentioned, such various factors as the lack of co-operation on the part of the patient, the improper use of ointments and lotions, the absence of natural or acquired immunity in the individual, and the failure to eliminate all the residual foci of the fungus are possible explanations of this recalcitrance.

It will be recalled that the dermatophytes usually grow best in the keratin layer of the skin including the keratin of the hair and nails as well as that in the folds of the body and in the moist, alka line environment. It is therefore essential frequently to cleanse the affected area with cotton or gauze soaked in a little vinegar and follow it with a keratolytic ointment.

An example of this lack of response to treatment is the man who responded satisfactorily although slowly to treatment with x-rays and Whitfield's ointment. He had faithfully followed instructions by vigorously rubbing the ointment into the lesions on his arms, legs, and feet with a towel wrapped around the hand. Improvement, as stated, had been satisfactory until a crop of dermatophids appeared on the extensor surfaces of the arms and legs. An examination of the feet revealed the presence of several active lesions which he had neglected to treat. The patient was told to omit all treatment but that of the moist areas on the feet. He returned to the office two weeks later happy over the disappearance of the spots and the itching In this instance as in so many others, the residual foci of fungi on the feet were undoubtedly the cause of the patient's failure to respond completely to antifungal agents.

The importance of rubbing the ointment with great force into affected nonhairy areas at least twice daily can not be overemphasized. Its efficacy is enhanced if the hands and feet are first placed in a weak solution of vinegar and the body lesions are daubed with a cloth soaked in the same. Persistence in following this regimen usually results in a cure, especial attention being paid to any reservoir of infection.

The indications for using solutions of potassium permanganate and cold compresses of solution of aluminum actetate N.F in acute stages of mycotic disease are too well-known to merit discussion. Hairy regions are best treated with solutions of various

composition. I have found Castellani's paint and Squibb s Mycostatin in ointment or capsules of 500,000 units equally effective against Candida infections under the breast and elsewhere.

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18

Tuberculosis of the Skin

By
Gustav Riehl

A CUTANEOUS lesion produced by Mycobacterium tuberculosis is currently called a tuberculoderm. This term also includes tuberculous lesions of the mucous membranes of the mouth, nose throat, and anogenital region.

Although the clinical picture of the tuberculoderms is well-known and clearly defined, the diagnosis can not always be confirmed either by histologic examination or immunologic tests. The immunologic situation of the host tissues, for instance may prevent the development of classic tuberculous structure. Extreme hypersensitivity and complete lack of sensitization to the tuberculous toxin are well illustrated in patients with tuberculous septicemia, on the one hand, and in those with complete anergy and lack of tissue reaction on the other

Either Moro's test or the more accurate Mantoux test may be used in diagnosis. A negative reaction means that the subject either has not had tuberculosis or is overcome by a virulent tuberculous infection and is unable to respond to tuberculin Examples of the latter are generalized miliary tuberculosis and mucocutaneous tuberculosis The "positive anergy" displayed by patients with Boeck's phase of cutaneous sarcoidosis is regarded as an exception to this dictum by those who believe in the tuberculous origin of sarcoidosis On the other hand, a positive reaction means that the patient harbors living bacilli in his body It does not indicate, however that the skin lesions are tuberculous the occurrence of focal reactions in these lesions will alone confirm this. Patients displaying a positive response do not as a rule show ac-

tivation of existing skin lesions The dangers of high-dosage diag nostic tuberculin are too well known to merit consideration.

It is impossible to distinguish clinically between the lesions produced by the human and bovine types of M tuberculosis. The avine type of bacillus, however is responsible for characteristic pictures. Bovine tuberculosis has been almost completely eradi cated in the United States, which probably accounts for the relative rarity of cutaneous tuberculosis in that country This low incidence of cutaneous tuberculosis is also found in other parts of the Americas, in spite of the great number of infected cattle and of patients with pulmonary tuberculosis.

It was recently demonstrated that many strains of bacilli culti vated from the skin lesions of this disease fail to show the morphologic and cultural features which we have learned to associate with infections caused by either the bovine or the human type of bacillus. Instead, they show features of both types. Funk has shown that the virulence of the particular strain of bacillus does not determine the type or degree of malignancy of the skin lesion.

The nature of the chemical substance responsible for tuberculous and tuberculoid infiltrates is well established. Twenty to 40 per cent of the dried bacillary material consists of lipid substances, and the remainder of carbohydrates, albumins, and pigments. Three lipid fractions have been found the acetone-soluble fat, phosphatides, and the waxes The epithelioid cells are apparently produced by the action of substances contained in the phosphatides and fat, which accounts for the ability of dead bacilli to evoke specific tissue reaction. Roulet and Block maintain that this substance is d phthionacid.

With the development of immunity many bacilli are destroyed by polymorphonuclear leukocytes, and d-phthionacid is liberated from these dead bacilli. It is then dispersed in the cytoplasm of histiocytes, resulting in their transformation into epithelioid cells. These subsequently phagocyte the remainder of the living bacilli as well as the dead bacilli and thereby are destroyed. According to Kalkoff giant cells resulting from further irritation of epithelioid cells by d phthionacid represent the final step in the prolifera tive phase of the disease.

Individual local and general factors cause different reactions of the host tissues, thus producing differences in the clinical picture. The skin is apparently not a fertile field for the growth of the organism, either because of its irregular and comparatively low temperature or because of its peculiar structure. The reaction of the skin differs only slightly from that of other organs, with the formation of foci of caseation necrosis surrounded by a zone of epithelioid cells and occasional giant cells These tubercles are more or less walled off from the adjacent tissue by a thin band of lymphocytes. The occurrence of necrosis in the skin is extremely rare.

Irregularities in the structure of the tubercle are frequently found, these depending on the immunologic situation of the host. Plasma cells are never present in profusion. The elastic fibers resist destruction much more than in syphilis.

The bacillus enters the skin in three ways from the outside, through the lymph channels, and from the blood stream. The rare primary complex of the skin is the best example of exogenous infection. Verrucous tuberculosis of the skin, on the other hand, also occurs as an exogenous infection but only in patients who have already been infected, thereby representing a reinfection. In mucocutaneous tuberculosis, the resistance of patients is low and the tissues swarm with bacilli, resulting in reinfection in the terminal stages of pulmonary or intestinal infection.

The primary complex may change into lupus vulgaris. *Children living intimately with tuberculous individuals may develop* lesions on the buttocks, which we in Austria call crawling lupus. I have seen indurated edematous lesions of the female genitalia produced in this manner These lesions, however are extremely rare.

In 70 per cent of patients with lupus vulgaris, the infection develops as a result of the spread of the infection from neighboring lymph nodes, bones, cartilage, or tendon. Colliquative tuberculosis of the skin develops in this manner The way in which the underlying lymph node becomes infected is still open to conjecture. Milk and milk products may be the answer In this connection, it will be recalled that pasteurization does not completely protect against infection and that bacilli can thrive in sour milk where they may remain viable for many weeks. Persons drinking

contaminated milk may therefore become infected in any part of the mouth, the frequent involvement of the deep cranial lymph nodes of the neck indicating that the tonsils are often the site of the primary complex. The tonsillar chancre may not be evident on inspection.

The skin in the remaining 30 per cent of patients with lupus becomes infected through the blood stream. This is also the mode of production of the tuberculids. Dissemination by the blood stream in lupus usually occurs only once in the lifetime of the individual. The foci produced in this manner are occasionally difficult to distinguish from those arising from infected lymph ducts or nodes Futhermore, it is often impossible to find clinical evidence of involvement of other organs in instances of extensive lupus produced by blood borne dissemination. Hist. lung examination of the bronchial and hilar lymph nodes, however usually shows structural changes typical of tuberculosis.

It is generally believed that M tuberculosis localizes in the dermis and subcutaneous tissue in which the blood vessels do not respond normally to certain stimuli. As a consequence of this abnormal vascular reactivity characterized by relative deficiency of oxygen and sluggish circulation, the bacillus lodges in the dilated and atonic minute vessels, whence it gains entrance into the interstitial fluids. Thus almost all forms of cutaneous tuberculosis have their origin in and about the arterioles and minute [illegible] of the subcutaneous tissue and dermis.

Since the arterioles leading to these dilated minute [illegible] innervated by sympathetic and parasympathetic nerve [illegible] follows that an autonomically unstable individual, ha[illegible] culous focus in his body runs a better chance of de[illegible] tuberculosis than a tuberculous individual who is [illegible] stable. This would explain the occurrence of erythema [illegible] in women showing signs of autonomic unbalance [illegible] by their abnormal response to cold, as well as the [illegible] the papulonecrotic tuberculid almost exclusively [illegible] with cold, cyanotic hands and feet, also indicating [illegible] instability The predilection of lupus vulgaris for [illegible] tributed by many to the increased capillary perme[illegible] by autonomic unbalance as shown by the grea[illegible]

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subsequent development of acute miliary tuberculosis, the spontaneous healing of the lesion with calcification of the regional lymph nodes, and the development of erythema induratum and the papulonecrotic tuberculid resulting from the dissemination of the infection by the blood stream. I have never seen the primary complex occur in adults following a slight abrasion from jumping into a swimming pool as reported by Hellerstroem.

Miliary tuberculosis of the skin occurs in early childhood as an expression of generalized miliary tuberculosis. The lesions consist of slightly elevated papules ranging in size from a pinpoint to 5 mm. in diameter occurring singly or in groups. These maculopapules, some of which contain specks of blood, usually break down to form ulcers covered with a dirty crust. The little patients show a negative response to intradermal tuberculin, bacilli are abundantly present in the skin lesions.

Lupus vulgaris makes its appearance as a flat, inconspicuous, brownish-red spot about the size of a barleycorn. It is soft and transparent, being readily punctured when slight pressure is applied with a blunt metal probe. Most of the other features of lupus, such as the apple jelly nodule, the absence of caseation necrosis, the tendency to form verrucous growths and superficial elevations, and the occasional development of squamous-cell carcinoma are universally well-known and recognized. The ability to form new lesions in the sunken, depigmented scars distinguishes these scars from those of syphilis.

Lupus vulgaris erythematoides is a rare variant of the disease which is difficult to distinguish, on clinical grounds from lupus erythematosus. A histologic examination is usually required to settle the matter

Lupous infiltrates of the mucous membranes of the mouth begin as tiny grayish-brown, slightly transparent, soft spots. They rapidly grow into relatively large granulomatous lesions which readily break down to create soft ulcers with overhanging borders. The ulcer base, which is usually covered with purulent material, is formed by nodules which have lost the epidermis. Various degrees and types of mutilations may result from extension of these ulcers. Fortunately however modern treatment and Public Health measures have greatly reduced their incidence.

A little-known complication of lupus is recurrent erysipelas, occurring in patients with lymphatic stasis resulting from the pressure of constricting scars on bones and other structures. The explanation of the occurrence of elephantiasis following repeated bouts of erysipelas, lies in the fibrotic obliteration of the lymphatic channels.

My experience with carcinoma in lupous lesions leads me to believe that it is a rare complication in patients who have not received treatment. The old question as to whether the use of x-rays and radium brings on malignancy is difficult to answer However an analysis of the patients who have come under my care does not indicate that these therapeutic agents are more carcinogenic, if at all, than others, such as the Finsen light or cauterization. Neither is it admissible to conclude from this material that carcinoma in these patients tends to metastasize to other organs or to recur after appropriate management.

The rare occurrence of lupus vulgaris following a vaccination with BCG was recently observed by Schmidt. A 12 year old boy was inoculated on the left arm with BCG vaccine. One month later a brownish spot appeared at the site of the inoculation, which gradually increased in size and became indurated. When examined by the observer two years after the inoculation, the lesion was irregularly round and measured 4.2 cm. in its greatest diameter The histologic examination of biopsy material revealed a typical lupous infiltrate. Treatment with isonazid and streptomycin effected a cure in three months

The results of extensive surveys of patients with lupus in Germany indicate that these individuals more frequently acquire pulmonary tuberculosis than those without cutaneous involvement, although the course of the disease in these patients is benign. These observations have led some investigators to induce lupus in patients having active pulmonary tuberculosis, hoping thereby to inactivate the process. After observing a large number of patients who were treated in this manner elsewhere, I have come to the conclusion that they would have been better off without the inoculation of lupus material, since it is quite evident that skin tuberculosis does not exert a curative effect on tuberculosis of the lungs.

Tertiary syphilis must always be differentiated [illegible]. Here the clinical features are more important than [illegible], with the exception of the vascular changes and the [illegible] the elastic tissue to withstand destruction. This is especially [illegible] in sections of tuberculous material dominated by [illegible] necrosis, in which there is complete destruction of all [illegible] elements.

The lesions of lupus miliaris disseminatus faciei (L.M.D.F.) consist of small, discrete, brownish-red papules [illegible] or in groups. These papules, often showing a [illegible] the presence of caseation, are situated in the upper part of the dermis, where they form around the papillary network of [illegible], blood vessels. The disorder is distinctly benign, healing [illegible]taneously in most instances. The response of patients to [illegible]dermal tuberculin is negative at first, tending later to become positive.

In the American Negro, there is a tendency of this disorder to involve large areas of the skin.

In the differential diagnosis, disseminated lupus vulgaris, papular rosacea, the micropapular (rosacealike) tuberculid, the [illegible] papular phase of cutaneous sarcoidosis, and eruptions caused by iodine or bromides should be considered.

Many North American dermatologists do not believe that L.M.D.F., the micropapular tuberculid, or papular rosacea has anything to do with tuberculosis. Layman and Michelson, for instance, are more conservative in requiring the fulfillment of certain strict criteria for tuberculosis before establishing a definite diagnosis of the micropapular tuberculid.

Tuberculosis verrucosa cutis or necrogenic wart is a relatively infrequent disorder occurring mainly in patients with active pulmonary tuberculosis who rub the infection into their fingers or the back of their hands. The disease occurs in individuals whose skin is nearly immune to the bacillus, representing, as previously mentioned, a reinfection. The lesions consist of wartlike hyperkeratotic patches surrounded by an inflammatory halo. Pus may be expressed from the crevices separating the warty growths where the pus originates in micro-abscesses caused by staphylococcal contamination.

In the differential diagnosis, the verrucous and multilocular forms of lupus vulgaris and certain forms of the common wart should be considered. In the Americas, confusion may arise with verrucous forms of chromoblastomycosis.

Mucocutaneous tuberculosis is characterized by small, shallow ulcers with undermined overhanging borders, occurring mainly about the mucous orifices of patients who are in the last stages of *pulmonary laryngeal, or intestinal tuberculosis. The ulcers usually become confluent* and form large, irregularly-shaped, shallow ulcerations with a granulating base having tiny grayish-yellow spots. The ulcers yield bacilli in profusion. The response of these patients to intradermal tuberculin is negative.

Atypical localizations of the ulcers may occasionally occur They are due to dissemination of bacilli by the blood stream and *not to the rubbing of the infection into* the skin or mucous membranes with the hands, as in the case of typical orificial ulcers.

The similarity of these ulcers to those found in patients with microtuberous tertiary syphilis is striking. In doubtful instances, the therapeutic test for syphilis and the histologic examination will settle the matter

THE TUBERCULIDS

The following three disorders are true tuberculids erythema induratum the papulonecrotic tuberculid, and lichen scrofulosorum.

Erythema induratum is a chronic disease occurring mainly on the lower portions of the calves of women. Children are never affected, which is a point of distinction between *this disorder* and erythema nodosum. *Guinea pig inoculation is often necessary* to differentiate erythema induratum from other nodose lesions of the extremities.

The capillary microscopic examinations of these bluish-red infiltrations shows dilated minute vessels through which the rate of blood flow is diminished. The skin temperature is lowered as a result of the sluggish circulation.

The papulonecrotic tuberculid is characterized in its early stages by bluish-red papules lying just beneath the surface of

the skin. In more advanced lesions, the papules protrude above the level of the skin and show central necrosis. The usual eruption consists of 10 or more perifollicular papules scattered over the extensor surfaces of the legs. Healing takes place with formation of a small, round scar and a residue of *pigmentation.* Occasionally however central necrosis does not occur and involution takes place without scarring.

Variants from this classic type of eruption are numerous, both as to morphology and localization. The lesions may be deeply situated and covered with normal skin, later breaking down to form large ulcers. This type represents a transitional phase in the development toward erythema induratum. Bullous and hemorrhagic elements may occur Other sites of predilection are the gluteal region, the extensor surfaces of the arms, hands, fingers, and occasionally the trunk.

As in many other forms of cutaneous tuberculosis the early involvement of the small blood vessels of the skin is evident in the papulonecrotic tuberculid. A definite degree of vascular predisposition and a sluggish circulation exist in patients with this disorder as is shown by the presence of acrocyanosis and the tendency to chilblains. Because of this, it is occasionally difficult to differentiate chilblain from erythema induratum.

The distinction of this tuberculid from such various disorders as acne, acne conglobata, papular rosacea, varioliform parapsoriasis, lupus miliaris disseminatus faciei, and the micropapular tuberculid, is occasionally difficult to determine. The histologic changes in most of these disorders are somewhat similar

Lichen scrofulosorum is a rare occurrence in my experience. It represents the response of children to the dissemination of bacilli to the skin by means of the blood stream. The lesions consist of pinhead-sized, soft, skin-colored, flat or acuminate papules, occurring in groups on the trunk. Occasionally the papules are covered with a fine scale. Itching is absent, and the eruption heals spontaneously within a few months.

For the purposes of this book, it will suffice merely to mention several disorders possibly caused by M. tuberculosis or its products. They are cutaneous sarcoidosis, lichen nitidus, and pustular dermatitis of the hands and feet occurring in winter (Crocker)

Likewise brief mention is made of avine tuberculosis of the skin. This malignant type of tuberculosis of the skin is fortunately infrequent. Four types of this disorder were described by Urbach sarcoidlike subcutaneous nodules, ulcers following septicemia, gummatous lesions and solitary ulcers generally ascribed to inoculation of the infection in persons employed on poultry farms.

TREATMENT

The introduction of calciferol, streptomycin, para-aminobenzoic acid, thiosemicarbazone, and isoniazid in rapid succession as antituberculous agents of highest efficiency is one of the medical wonders of the ages

Isoniazid has proved to be the most effective of these drugs. Its use has practically solved the problem of cutaneous tuberculosis There remains only the Public Health angle. The personnel of the local Public Health Departments should be instructed in ferreting out patients with fresh lesions of the disease and in carrying out measures of prevention. These measures include the eradication of the disease in cattle as well as accurate follow up services to prevent recurrences of the disease in human beings.

The management of severely disfigured patients, fortunately only rarely necessary in the Americas, has been greatly facilitated by plastic surgery and cosmetics.

Isoniazid is effective, nontoxic, and has the great advantage of being suitable for ambulatory therapy On account of this feature, the large European sanatoria for the care of patients with tuberculosis of the skin are rapidly being emptied. The contra indications to the use of the drug are practically nonexistent.

Isoniazid is administered in 50 mg. tablets of Nydrazid, the dosage averaging 5 mg per kilogram of body weight per day The tablets are best taken with meals. A light diet is prescribed, consisting mainly of milk, white meat, vitamins and small amounts of carbohydrate. Salt and spices are prohibited. Urinalyses should be made weekly and a hemogram, monthly

No instance of intolerance to the drug was observed in my patients. An increase in weight occurred in most patients and

a feeling of well being was also experienced. This desirable side-effect is probably due to the action of the drug on the central nervous system.

Higher doses have been advocated by some to increase the effective action of the drug Marchionini, for example, gives his patients as much as 15 mg per kilogram of body weight. Although the incidence of toxic reactions is no higher with these doses than with what I use the percentage of relapses occurring after one year is the same as in my series of cases.

The untoward side-effects of isoniazid in 10 per cent of 2300 patients with pulmonary tuberculosis reported by Fust and his collaborators were of a mild nature, including dizziness, constipation, headache, and slight sensory and motor disturbances.

The formation of resistant strains of the bacillus in patients with pulmonary tuberculosis, following the use of isoniazid was reported by other investigators. To prevent the development of resistance, the so-called swing therapy was introduced. It consists of the alternating use of isoniazid and other therapeutic agents, such as para-aminosalicyclic acid and streptomycin. It was found that strains which had become resistant again responded to isoniazid after a period of this swing therapy

Resistance to the drug did not develop in my series of over 400 cases. In my opinion, this is due to the circumstance that the storage capacity of the skin for isoniazid is greater than that of the viscera.

The most favorable results are obtained in patients with lupus vulgaris in which the lesions usually show signs of involution within a period of three months The treatment is then continued for another 45 days. It is gratifying to observe the rapid flattening of hypertrophic lesions as well as the speedy epithelialization of ulcers both of the skin and mucous membranes. The excellent cosmetic results obtained in the healing of these ulcers are truly remarkable. Patients with colliquative tuberculosis respond equally well to isoniazid, although somewhat slower These results are in agreement with those of Latapi and his coworkers.

Fluctuating lymph nodes should be incised and drained. Other forms of cutaneous tuberculosis, particularly those which formerly

were resistant to treatment, also respond well to isoniazid at first. This applies especially to erythema induratum, in which, however it is occasionally necessary to combine the drug with streptomycin. Relapses in patients with this form of tuberculid as well as with other tuberculids are unfortunately not uncommon. Recurrences may occur during the administration of the drug The occurrence of granuloma annulare during treatment mitigates against a tuberculous origin. In my experience, patients with Boeck's phase of sarcoidosis respond favorably although relatively slowly to isoniazid. The improvement observed in patients with lichen planus speaks strongly for a nonspecific pharmacologic action of the drug in addition to its specific action against M. tuberculosis.

The three patients with disseminated miliary lupus of the face who have so far come under my observation have failed to respond to isoniazid. It will be interesting to see if all patients with this disorder fail to improve with the use of this drug, and if so, why?

The specific action of the drug persists for a long time, particularly against strains which are resistant to streptomycin para-aminosalicyclic acid, or thiosemicarbazone. The ability of isoniazid to pass through membranes greatly enhances its value in the treatment of tuberculosis of the central nervous system. It probably also accounts for the feeling of well being in these patients. The chemotherapeutic index of the drug is 44 as compared with 16.5 for thiosemicarbazone, and 39 for streptomycin.

Optimum results in the eradication of cutaneous tuberculosis will be obtained by including patients with lupus erythematosus in the Public Health aspects of tuberculosis. In such countries as the United States, where the incidence of cutaneous tuberculosis is low these Public Health measures could be directed mainly if not exclusively to the care of patients having lupus erythematosus.

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19

Leprosy Symptomatology, Diagnosis, and Treatment

By
Arturo Romero

THE INCUBATION period of leprosy is extremely variable, ranging from three to five years in most cases. Children are most susceptible to infection, although the incidence of clinical symptoms is greatest between the ages of 20 and 40 years. The youngest patient in my experience was five years old and the oldest over 100 The disease affects children of both sexes equally although after puberty the incidence of infection in males rises to 60 per cent. Women usually experience exacerbations at puberty the menopause, and during pregnancy and childbirth.

Leprosy affects all classes of society with a predilection for the poor the latter showing a higher infection-incidence because of their crowded living conditions Poorly nourished persons and those working under unhygienic conditions are also liable to be affected.

Hot, moist localities take the highest toll of victims, although a breakdown of statistics indicates that the presence of focal areas of the disease is actually due to unhygienic living conditions and other factors previously mentioned

The early signs of leprosy are extremely variable consisting of constitutional symptoms of fever anemia, weakness joint pains, aching bones and cutaneous lesions of various kinds. These early manifestations are rarely observed by the physician the patient usually not seeking medical aid until long after the initial symptoms have disappeared.

The most frequently noted early signs are cutaneous areas of paresthesia and anesthesia, depigmented, red, or grayish macules

loss of the eyebrows and lashes, and retinitis. In more advanced cases, nodules are sometimes found on the face, arms, or legs, associated with neuritis. At other times, there are trophic disturbances, such as perforating ulcer of the foot, episodes of erythema multiforme, fever arthritis, osteitis, or vasomotor disturbances Bullous and keloidal lesions are rarely encountered in Costa Rica. Once these symptoms have appeared, they rarely disappear spontaneously

The chronic and progressive course of the disease is punctuated by acute febrile episodes which are associated with exacerbations of the existing symptoms In addition, the occurrence of eruptions resembling erythema multiforme or nodosum or of necrotizing lesions with resultant ulcerations is frequently observed.

The neural lesions are expressed clinically by disturbances of sensation, first of temperature, then of touch and pain. In advanced lesions, involvement of the large peripheral nerves of the extremities frequently leads to clawlike deformities, hypoesthetic run-arounds, chronic mutilating osteitis, and trophic ulcerations.

The most frequent complications of leprosy are those involving the eyes, larynx, testes, ovaries, kidneys, liver spleen, and lymph nodes. The eyes are most commonly affected by iritis and iridocyclitis blindness is frequently the result of these complications. Conjunctivitis and keratitis are not infrequent.

Pharyngitis and ulcerative laryngitis are serious complications particularly the latter which can cause death by suffocation.

Involvement of the testes and ovaries is manifested at first as inflammation associated with intense pain, later resulting in sterility Renal involvements results in nephrosis or nephritis the latter complication seriously affecting the prognosis. The liver often becomes enlarged but rarely shows functional disturbances. Enlargement of the spleen and lymph nodes is common.

Leprosy runs a precocious course, sometimes assuming a mild form resulting in spontaneous cure, at other times remaining stationary for a long time without signs of activity and then again appearing in malignant forms associated with prolonged febrile episodes which weaken the patient and ultimately cause his death. Not infrequently an intercurrent infection terminates it.

I shall confine myself to a consideration of the salient and diagnostic clinical features of each of the three basic types of leprosy observed in Costa Rica.

LEPROMATOUS TYPE

This type constitutes 64 per cent of all Costa Rican cases of leprosy

In 50 per cent of cases lepromatous leprosy begins with lesions of the nasal mucosa associated with loss of the eyebrows and lashes in 35 per cent, with sharply demarcated, grayish, flat infiltrations occurring especially on the face and extremities; in the remaining 15 per cent, with ill-defined infiltrations which become nodules limited to the face and extremities.

Depending on its onset and subsequent course, lepromatous leprosy may be divided into three forms, diffuse, infiltrative, and nodular

1. *Diffuse lepromatous leprosy* This form begins with rhinitis and loss of the eyebrows and lashes and is associated with the constitutional symptoms previously mentioned. Associated signs of this form of the disease are generalized anesthesia of the skin, loss of hair on the arms and legs, little or no sweating, and positive bacteriologic findings in material taken from any part of the skin.

Anesthesia is usually not pronounced at first. The skin has a wrinkled appearance as in ichthyosis, the skin of the face appearing thin, transparent, and stretched, all of which, with the red nose and the ears pressed against the head, gives the impression of a wax mask.

The loss of hair spreads from the eyebrows and lashes to the hair of the body and scalp leaving semicircular areas of alopecia on the scalp and back of the neck.

Dilated blood vessels are seen coursing over the cheekbones, forehead, and thighs.

There is a constant hemorrhagic discharge from the nose The nasal septum is finally destroyed, leaving the nose flattened. Vegetating growths, yielding bacilli on microscopic examination, usually obstruct the nasopharyngeal air passages. The larynx is relatively unaffected.

In spite of involvement of other structures, the eyes are not affected other than by conjunctivitis due to the irritation caused by the lack of eyelashes

The downward course of diffuse lepromatous leprosy is hastened by repeated bouts of fever and crops of lesions consisting of superficial necrosis of the dermis, with capillaritis, hemorrhage, and flaccid blisters occurring on any part of the skin. These lesions are associated with aching bones and joint pains and constitute Lucio's phenomenon. It is characteristic of these eruptions that they appear without fever and that they heal with scarring or ulceration, depending on the depth of cutaneous involvement.

The bouts of fever last for several months and are marked by temperatures of 39 C. or 40 C. The attack is initiated by chills and intensely aching bones which are *not associated with eruptions resembling erythema multiforme*. Patients with attacks of fever of this nature, when given sulfone medication, soon cease to have fever but develop eruptions resembling erythema multiforme.

The diagnosis of typical cases is readily made on the clinical symptoms and the positive histamine test.

The occurrence of Lucio's phenomenon serves to confirm the diagnosis of diffuse lepromatous leprosy since bacilli are found in all parts of the skin.

The diagnosis is difficult in cases beginning with weakness, edema of the legs, intermittent attacks of fever, or rheumatic pains. Such cases require a high degree of awareness on the part of the observer to make a correct diagnosis.

The occurrence of eruptions resembling erythema multiforme should occasion a careful search for etiologic factors, with particular emphasis placed on leprosy in countries where leprosy is prevalent.

2. Infiltrative lepromatous leprosy In this form, patches of infiltration usually appear first on the face and extremities, associated at times with partial loss of the eyebrows and lashes and of the hair on the arms. Although the affected area of skin yield the bacillus, the nasal mucosa often does not. The peripheral nerves are thickened and palpable, and clawlike deformities and mutilating lesions of the fingers and toes make their appear-

ance early in the course of the disease. The cutaneous lesions consist of grayish or copper-colored, anesthetic infiltrations with ill-defined borders. Involvement of the skin of the cheekbones, forehead, and ear lobes serves to accentuate the wrinkles in the forehead and causes the arms and hands to appear puffy

This form of leprosy runs a chronic course, punctuated by bouts of fever and eruptions resembling multiform or nodose erythema. Patients affected by these episodes of reactional leprosy are in apparent good general condition in the intervals between episodes.

The eyes, larynx, and testes frequently participate in the general disorder the eyes developing iridocyclitis which may result in blindness and the larynx developing laryngitis which may cause stricture and sudden death from suffocation.

The diagnosis is confirmed by positive findings of sensory disturbances and bacilli in the cutaneous areas of infiltration.

Positive serologic tests in these patients give rise to the possibility of syphilis, although a consideration of the symptoms and signs previously enumerated readily excludes the diagnosis of syphilis.

3. Nodular lepromatous leprosy Material obtained from the nasal mucosa of patients with this form of the disease does not always contain bacilli. These patients may show partial loss of the eyebrows and lashes when the lepromas are located in the skin immediately above these structures. Their general condition is good.

The lepromas vary in size from a few millimeters to a centimeter or more in diameter are located mainly on the face and extremities, and are usually anesthetic. The color of the overlying skin is normal or pale red. Lepromas which are firm and painless may be few or numerous discrete or confluent, when confluent and present on the face the patient has a leonine aspect.

The organs participating in this form of leprosy are the same as those affected by infiltrative lepromatous leprosy Bilateral osteitis with clawlike deformities and eruptions resembling nodose and multiform erythema are usually found.

The differential diagnosis of nodular lepromatous leprosy includes among others, von Recklinghausen's neurofibromatosis

and the lesions of the nodular phase of [illegible] conditions may be excluded by the characteristic [illegible] ated with the nodular form of lepromatous lesions.

TUBERCULOID TYPE

Tuberculoid leprosy has an insidious onset [illegible] at times, of one or more slightly raised, [illegible] lichenoid or annular medallions devoid of sensation [illegible] in size from 1 to 5 cm. in diameter. Those of [illegible] tion have a clear center with erythematous [illegible] Subjective symptoms are absent. The lesions [illegible] part of the skin. The peripheral nerves are [illegible] cases.

At other times, the disease manifests itself as:

1. One or more raised, well-defined, [illegible] associated with sensations of burning, formication [illegible] pain. The peripheral nerves are thickened, [illegible] volvement of the interosseous muscles and [illegible] and hypothenar eminences results in clawlike [illegible] ties.

2. Neuritis and thickening of the peripheral nerves, particularly of the ulnar nerve, resulting in retraction-deformities [illegible] hand.

3. A sudden eruption of numerous cutaneous [illegible] ated with peripheral neuritis, intensely aching bones and early development of retraction-deformities of the extremities.

4. Cutaneous lesions, associated with neuritis of the [illegible] just described, arise in patients in whom the history reveals the previous occurrence of chronic lesions of the skin, typical of leprosy.

Depending on the form in which it first shows itself tuberculoid leprosy may be divided into minor and major forms.

Minor form. This variety consists of papular lichenoid or annular medallions devoid of sensation. The lesions are un- associated with neural involvement.

Major form. This variety comprises cases starting with well-defined, red patches which are hyperesthetic at first, then anesthetic, and which are associated with subjective symptoms of

varying severity The peripheral nerves are markedly thickened. The onset in some patients is signalized by the occurrence of neuritis and deformities.

Both forms of tuberculoid leprosy have episodes of reaction, during which the presenting lesions become aggravated, and new lesions appear associated with intensely aching bones, neuralgia, and bouts of fever the attack frequently resulting in the formation of deformities. The lepromin test remains positive and a few bacilli are temporarily found on microscopic examination.

The cutaneous adnexa and viscera do not usually participate in tuberculoid leprosy Involvement of the muscles and tendons, however is frequent, often resulting in deformities and disfigurements, while absorption of bone produces mutilations of the fingers and toes.

Many patients with tuberculoid leprosy recover spontaneously without showing the least trace of the infection. The lesions in both the minor and major forms first begin to pale in the center and show a light scale, after which they disappear and heal with depigmentation. Sensation usually recurs in the healed lesions after the lapse of time. Reactional leprosy causes irreparable damage.

The erythematous, well-defined infiltrations of the tuberculoid type occasionally cause confusion with erysipelas. The papular and lichenoid medallions may resemble fungous lesions, certain tuberculids, the herald spot of pityriasis rosea, or syphilitic lesions. Annular and circinate lesions often resemble fungous, tuberculous, or syphilitic lesions but are readily distinguished from them by the characteristic signs of leprosy In some cases, however recourse to biopsy examination and the lepromin test is necessary

The differentiation of neural leprosy from neuritis caused by other agents is aided by the occurrence of muscular atrophy in the area innervated by the affected nerve. Biopsy examination of the nerve is required in patients who do not have cutaneous areas of anesthesia.

Reactional tuberculoid leprosy is usually easily detected by evaluation of the clinical symptoms and biopsy examination.

INDETERMINATE TYPE

This type may start with a solitary erythematous or depigmented, flat patch of variable size, occurring particularly in the gluteal regions or on the thighs, arms shoulders, chest, or neck. The patient's health is not affected, and he usually takes little if any notice of the spot on his skin. The histamine test is positive, and clawlike deformities usually occur

At other times, this type first shows itself as anesthetic areas of skin, without the patient being aware of his condition until one day he burns himself without feeling it. Sometimes the first indication of the disease is a deformity caused by involvement of a nerve, with resultant muscular atrophy and retraction of tendons. Trophic disturbances occur frequently and perforating ulcer of the foot is sometimes found in association with clawlike deformities. Adnexal and visceral lesions are uncommon. Both the lepromin test and bacteriologic examination of material taken from the lesions may be positive or negative.

Patients with this type of the disease sometimes develop in the skin diffuse infiltrations containing numerous bacilli, indicating the transformation to lepromatous leprosy At other times, the development toward tuberculoid leprosy is shown by the sudden appearance of a crop of bright red, well-defined lesions associated with neural involvement. Instead of developing lepromatous or tuberculoid leprosy these patients often remain in the indeterminate group indefinitely

As a rule, patients initially having a positive lepromin test eventually develop tuberculoid leprosy while those with an initial negative test develop lepromatous leprosy

The diagnosis of indeterminate leprosy can usually be made on the clinical symptoms and laboratory findings taken in conjunction with the personal and familial histories. Occasionally however months of observation are required to establish the diagnosis.

BORDERLINE OR DIMORPHIC TYPE

I have observed only five patients with this type of leprosy and all five ultimately developed lepromatous leprosy The lepromin test was negative, and the bacteriologic examination of

material taken from the lesions and nasal mucosa was positive. This type resembles reactional tuberculoid leprosy in its cutaneous and neural manifestations.

TREATMENT

The sulfones are the drugs of choice in the treatment of leprosy The sulfone, diaminodiphenyl sulfone (DDS) and its derivative compounds are only bacteriostatic and consequently should always be supplemented with a nutritious diet and meticulous hygienic care.

The dose of DDS for adults varies from 100 or 200 mg. daily to 400 or 600 mg. given once a week without interruption. It may be given orally or intramuscularly The derivative compounds of DDS are given in doses three or four times larger It is best to increase the dose gradually

The patient's tolerance to the drug should always be determined by means of the hemogram, erythrocytic sedimentation rate, urinalysis, and periodic physical examinations.

Adjuvant treatment is recommended in all patients receiving sulfone medication for a long time. This should include, among other remedies, the use of iron, liver extract, lipotrophic agents such as choline methionine, and inositol, as well as vitamins, with the exception of vitamin A, since it frequently induces episodes of reaction or reactivation. In my experience, the use of nicotinic acid is effective in bringing about improvement in the patient's general condition.

Treatment of reactional leprosy Daily intravenous injections of solutions of tartar emetic in combination with large doses of vitamin B complex are effective in controlling the pain of aching bones and the discomfort associated with fever and attacks of erythema multiforme.

If the patient displays intolerance to tartar emetic or offers difficulties to intravenous medication trivalent antimony in daily intramuscular doses of 3 cc. may be used instead.

The use of vitamin B_{12} in daily doses of 1000 micrograms is effective in patients with acute attacks of neuritis, and ACTH and cortisone bring prompt relief in ocular complications or bouts of fever Pain is alleviated by steroid therapy The combined

daily use of cortisone in doses of 25 mg. every six hours, tartar emetic, vitamin B complex, and vitamin B_{12} in doses of 1000 micrograms has proved highly effective in the acute phase of reactional leprosy

In tuberculoid leprosy the sulfones should be given in amounts equivalent to one half of those used in other types of the disease. Adjuvant therapy with a high-calory diet and large doses of vitamins D and B_{12} have proved highly effective in my experience. Vitamin D should be given for six months and vitamin B_{12} for a month or more if necessary particularly in patients with neuritis.

Other forms of treatment. 1. Surgical intervention is required in patients with osteitis wide resection of diseased bone is usually indicated. 2. Early correction of deformities by physiotherapy and orthopedic management should be combined with sulfone medication. 3. Rehabilitation of leprous patients should be accomplished with full use of psychotherapy and occupational therapy 4. Prophylactic treatment with BCG for contacts is described by Fernandez.

19A

Leprosy Bacteriology, Immunology, Pathologic Anatomy, and Prophylaxis

By

Jose M. M. Fernandez

BACTERIOLOGY

Mycobacterium lepræ. The leprous bacillus belongs to the family of Mycobacteriaceae of the order of Actinomycetales of Schizomycetes

The bacillus usually appears as a straight or slightly curved rod from 2 to 6 microns in length and from 0.2 to 0.5 micron in width. It is acid-fast and only mildly pathogenic. It is capable of assuming various forms. Its inoculation into experimental animals does not produce pathologic changes comparable to those of human leprosy It is sometimes impossible to demonstrate the bacillus in putative leprous lesions with present methods of staining

The ability of the bacillus to stain red with carbol fuchsin was first made use of in the classic stain of Ziehl-Neelsen. Once stained, it resists decolorization by strong acids or by alcohol. It is Gram-positive and has affinity for basic dyes.

A peculiar feature of leprous bacilli is the tendency to form bundles of parallel rods and globular masses known as globi.

The distinction between Mycobacterium lepræ (M.l.) and Mycobacterium tuberculosis (M.t.) is difficult, due to the similarity of morphologic and staining characteristics. Current staining methods are notably deficient in the differentiation of these bacilli. In the same way animal inoculation and cultivation of M.t. upon artificial media are presently considered of little value because of the loss of vitality suffered by the tubercle bacillus from the widespread use of antibiotic and chemotherapeutic

agents. According to Malfatti, the distinguishing features of these organisms can only be brought out by the electron microscope.

Among the many structural variations from the customary rod-form of the bacillus are several small elements which are derived from division of the organism. This division varies from simple segmentation of the bacillus into two or three elements bound to each other by a kind of sheath to its disintegration into granules which usually appear in chains resembling those of streptococci or in pairs like diplococci. Occasionally they occur as single elements. They are best studied under the electron microscope.

Tinctorial variations from the customary acid fastness are characterized by acid-sensitivity which lacks the ability to retain carbol fuchsin. Bacilli with this staining property are cyanophilic and capable of assuming the shape of rods or granules.

The significance of these structural and tinctorial variations is open to discussion, since some authors regard them as resistant forms of the bacillus, while others look upon them as intermediary products of bacillary disintegration.

Wade demonstrated that certain granular forms are artefacts and result from the use of certain types of fuchsin for staining purposes.

The granular and acid-sensitive forms are most frequently found in reactional leprosy and in treated patients.

Clinical improvement in patients treated with the sulfones is marked by progressive disintegration of the bacillus, signalized by the formation of granules and distortions resembling nails, globular masses, and commas. Finally nothing remains but bacillary dust.

In my opinion, the granular forms and tinctorial variations, when present in moderate numbers in relation to the customary rodlike forms, represent normal evolutionary phases in the life of the bacillus. When, however, they predominate over the rod like forms, as occurs in treated cases, they should be regarded as degenerative forms.

The successful propagation of M.L. in successive cultures has not been accomplished. It is probable that more than one

investigator has succeeded in cultivating the organism but every attempt to confirm his work has invariably led to failure.

Hanks reasons logically that every attempt at cultivation is purely empirical and bound to fail because of our lack of knowledge concerning the metabolism of M.l. In his experimental investigations along this line, Gray demonstrated interesting differences in the metabolism of M.l., M t., and M. leprae murium.

The strains of M.l. hitherto obtained in cultures can be classified according to the macroscopic and microscopic characteristics of the cultures as follows acid fast chromogens, acid-fast nonchromogens, diphtheroids, and anaerobes.

It has not been possible to reproduce the classic picture of human leprosy by experimental inoculations in man or laboratory animal. The lesions frequently found at the site of inoculation can also be produced by the injection of dead bacilli, as occurs with lepromin, and are therefore not of practical significance.

On the other hand, several well documented instances of accidentally induced inoculation of human leprosy have been reported.

The Stefansky bacillus is the etiologic agent of murine leprosy It has a close structural and tinctorial affinity with M.l., being acid-alcohol-fast and Gram-positive. Furthermore, it closely approximates M.l in length, being 3 to 5 microns long with rounded ends It also occurs in granular form.

The Stefansky bacillus cannot be cultivated, but when it is introduced into rats, it produces lesions of the skin and lymph nodes after an incubation period of two to four months.

IMMUNOLOGY

The lepromin reaction. The modern immunologic study of leprosy began with the experiments of Mitsuda, who showed that the intradermal injection of an aqueous suspension of boiled or triturated lepromatous nodules evokes a delayed local response in patients with neural leprosy and no response in subjects with cutaneous leprosy

This observation has been repeatedly confirmed and constitutes an important determinant in the classification of the disease. Depending on the response to the lepromin test, patients

are classified as possessing a favorable prognosis if they respond positively and a poor prognosis if the reaction is negative. I was able to show in 1940 that the Mitsuda reaction is preceded in the vast majority of cases by an earlier tuberculinlike reaction.

Antigens for use in the lepromin test are of three types

1. Whole lepromin is composed of varying amounts of bacilli and tissue debris and processed according to the method of Mitsuda-Hayashi or the modification of Muir Rothberg, and others. This type of lepromin is most widely used because of the simplicity of its preparation. It is prepared by first boiling in physiologic saline solution for 30 to 60 minutes a few small pieces of material obtained from lepromatous lesions and then grinding the residue in a mortar Twenty cc. of the physiologic saline solution used in boiling are now added to each gram of this triturated residue, and the resultant mixture is filtered through gauze and mixed with 0.5 per cent of carbolic acid. This is then sterilized for 1 hour at 60 C

The Sixth Congress of Leprology held in Madrid in 1953 recommended the use of this lepromin for routine work.

2. Bacillary lepromin consists of antigen composed exclusively of a purified bacillary suspension made according to the recommendations of Montanes Dharmendra, or Olmos and me. This is the type of lepromin recommended by the Congress for investigative work.

3. Protein lepromin is made from purified soluble protein extracts of M.L obtained by filtration or precipitation.

Technique and reading of the results of the lepromin test. An intradermal injection of 0 1 cc. of antigen is made in the normal skin of the scapular region or of the outer surface of the thigh or arm. A twofold response is noted in the positive reactions

Fernandez Reaction (24 to 48 hours)

Positive. Infiltrated erythematous halo of 10 or more millimeters in diameter

Doubtful. Infiltrated erythematous halo larger than 5 mm. but less than 10 mm. in diameter

Negative. Infiltrated erythematous halo less than 5 mm. in diameter

Mitsuda Reaction (3d to 4th week)

Positive. Nodular infiltration larger than 5 mm.

Doubtful. Nodular infiltration less than 5 mm.

Negative Absence of reaction.

Results of the lepromin test:

In leprous patients Invariably negative in the lepromatous type positive in 90 per cent of the tuberculoid type, and negative or positive in equal numbers of patients of the indeterminate group.

In persons living in more or less intimate and prolonged contact with a patient who is bacteriologically positive, the response to these tests is generally positive while in those living with a patient having the tuberculoid type, the reaction is also usually positive but less intense.

In supposedly leprosy-free persons whether or not they live in endemic areas, the Mitsuda reaction is positive in 70 to 80 per cent of cases, while the Fernandez reaction is positive in a smaller number of cases.

Interpretation. The lepromin test is only useful in gauging prognosis and not in diagnosis.

A positive test in a leprous person indicates a certain degree of resistance to M leprae. Thus a positive test is usually found in benign types of the disease and a negative one in the malignant types.

The same holds true for persons living with a leprous patient, in whom a positive test also indicates a certain degree of resistance, should they at some future time develop leprosy

It is generally believed that the same prognostic criteria apply to the normal healthy individual as to contacts.

Nature of the lepromin reaction. The Fernandez reaction reflects a state of hypersensitivity to the proteins of M.L., due to previous contact with this or other acid fast bacilli. The hypersensitivity is neither obligatory nor specific.

The Mitsuda reaction indicates a state of resistance to the infection. Wade interprets it as expressive of the ability of the organism to react to the bacilli contained in the antigen. The reaction can be positive without previous sensitization having taken place It is nonspecific because it can be positive in persons who do not have leprosy and negative in advanced cases of the

disease. There is, however one constant feature of the reaction. It is always negative in lepromatous leprosy

The high index of positivity observed in healthy persons living in endemic areas was originally regarded as an expression of specific hypersensitivity to M.l. This concept was soon discarded, however when immunologic surveys revealed that healthy persons living in nonendemic areas showed a similar high index of positivity It then began to be suspected that a positive lepromin test in leprosy free individuals indicates hypersensitivity to any of the related antigens and that M.t. was the chief if not the sole antigen of this kind. This concept has been substantiated by Cummings and Williams with tuberculin and by my experiments with BCG

There are other acid-fast bacilli beside M.t. capable of inducing positivity Schujman succeeded in provoking a short lived Mitsuda reaction with antigen prepared from the Stefansky bacillus.

The Madrid Congress recommended that experiments along these lines be intensified in order to determine the significance of the reversal of the lepromin test from negative to positive.

HISTOPATHOLOGY

An organism invaded by M.l. may react indifferently favorably or unfavorably to the attack. Each one of these attitudes is characterized by definite clinical, histoanatomic and immunologic features which are representative of the three basic types of leprosy

The histologic changes consistently reflect the degree of reactivity of the reticuloendothelial cells, particularly the histiocyte, to the invading bacillus. If the organism is able to repel the infection, the histiocyte is transformed into an epithelioid cell capable of destroying the bacillus. If, on the other hand, the organism cannot repel the infection, the histiocyte changes into a Virchow cell, whereby the cytoplasm undergoes vacuolization, and the bacillus is pulled inside to live in symbiotic coexistence. These two types of cells—the epithelioid cell and the Virchow cell—characterize the two extremes of tissue reaction represented by tuberculoid and lepromatous leprosy respectively The in-

determinate type shows only lymphocytic infiltration which reflects the indifferent attitude of the organism to the infection.

The histopathologic examination is valuable in establishing the diagnosis and in classifying the different types.

Its diagnostic value is conclusive only in lepromatous leprosy since only here are the histologic changes specific. It has less diagnostic value in tuberculoid leprosy and practically none in the indeterminate type, except for the presence of bacilli.

The histologic changes observed in the indeterminate type consist of an inflammatory infiltrate usually composed exclusively of lymphocytes, to which a few fibroblasts and histiocytes are occasionally added. The cells of the infiltrate are disposed around the blood vessels, nerves, and sweat and sebaceous glands. This nonspecific tissue reaction has diagnostic value only in sections containing bacilli, which occurs in about 50 per cent of cases, and in sections showing characteristic nerve changes.

These pathologic changes may represent either the initial or the involutionary stage of the disease. Not only is a nonspecific lymphocytic infiltrate typical of the indeterminate type, but it also characterizes the involutionary stage of lepromatous leprosy

The lepromatous type is characterized histologically by such typical pathologic changes that its confusion with other disorders is difficult. The lesions owe their distinctive character to the presence of the Virchow cell and the acid-fast bacillus.

The *Virchow cell develops from the histiocyte. It varies in* size and has a large, pale nucleus. Its foamy aspect is due to the presence of clear spaces containing lipids and numerous bacilli.

The infiltrate consists of varying numbers of lymphocytes, epithelioid cells, plasma cells, and mast cells, the total number of these cells being always less than that of the Virchow cells. In older lesions, the infiltrate loses its original character the Virchow cells decreasing in number and the infiltrate becoming less dense. Finally it invades the surrounding tissue, where it destroys the structures in its path—the connective tissue, the sweat and sebaceous glands, the nerves, and follicles. Large areas of the dermis are frequently destroyed in this manner leaving a tumor like mass in its place. A thin strip of collagenous ground sub-

stance known as Unna's band separates this mass from the atrophic epidermis

The neural lesions consist of interstitial neuritis which begins with a perineural infiltrate and then invades the interfascicular connective tissue, ultimately to destroy the nerve fibers.

The structural changes occurring in the testes, eyes mucous membranes of the upper respiratory tract, liver, spleen, lymph nodes, and bone marrow affected by leprosy simulate those encountered in the skin. Participation of the eye and testis in the general disorder frequently results in serious damage.

During episodes of reactional leprosy an acute inflammatory reaction is superimposed upon the specific pathologic changes noted earlier To the inflammatory infiltrate are added capillary dilatation and interstitial edema.

The tuberculoid type is characterized mainly by a tuberculoid infiltrate whose most prominent feature is the epithelioid-cell tubercle which is surrounded by a zone of lymphocytes. Giant cells of the Langhans type are occasionally present in the center of the tubercle

The similarity of the tuberculoid infiltrate in syphilis, particularly of the gummatous type, in the systemic mycoses, sarcoidosis, and tuberculoid leprosy renders their differentiation extremely difficult at times. Nevertheless, Castano-Decond and Grieco showed that a thorough examination of sections of tuberculoid leprosy will usually reveal specific neural lesions which enable one to distinguish it from other diseases.

The histologic changes encountered in the so-called borderline type show alternating areas of lepromatous and reactional tuberculoid leprosy Bacilli are abundantly present. The mixed character of the pathologic changes in the borderline type often makes its distinction from lepromatous or tuberculoid leprosy difficult.

PROPHYLAXIS

Antileprosy campaigns should include the following measures

1. Selective isolation of bacteriologically positive cases. This is applicable to "open" cases only as long as they are bacteriologically positive. When they become negative they should be transferred from the sanatorium to the out-patient department to

receive ambulatory treatment. The indiscriminate isolation of every leprous patient is not scientifically justified and nullifies the objective of the campaign.

2. Treatment of all known cases of leprosy The twofold purpose of treatment is to render the "open" cases negative so that these patients may be returned to society thus freeing more beds for other "open" cases and to maintain negativity in the "closed" cases receiving ambulatory treatment in the out patient department.

The effective action and ease of administration of the sulfones have greatly increased the importance of prophylaxis in the fight against leprosy

The treatment with the sulfones of lepromin-negative contacts was suggested by Souza-Campos and by Carboni and me. The Madrid Congress recommended its use in these cases

3. Control and protection of the contacts. A thorough examination should be made of all persons who are or were living with leprous patients. This not only makes early diagnosis possible but greatly increases the chances of recovery and lessens those of spreading the infection. Examinations should be made for five years at intervals of a few months in those who are negative to the lepromin test and at slightly longer intervals in positive cases.

Two measures for the protection of lepromin-negative contacts were recommended by the Madrid Congress. They are, first, vaccination with BCG and second, preventive treatment with the sulfones of persons over 10 years of age who remain negative to lepromin in spite of having been vaccinated with BCG

In 1939 I proposed the use of BCG vaccine as a protective measure for these persons. I was able to make this proposal from observation of 123 healthy children with negative lepromin tests, in whom 92 per cent became lepromin-positive a month after intradermal vaccination with 0.15 mg. of BCG

This experience was amply confirmed by the studies of Souza Campos, Rosenberg, and Aun. These authors showed that the oral administration of BCG is as effective if not more so, than its intradermal injection.

There is no unanimity of opinion among leprologists as to technique or dosage. Souza Campos gives 200 mg. by mouth weekly

for three weeks. However experience has demonstrated that smaller doses given at varying intervals are equally effective.

Granted that a positive lepromin test is our objective, and since it is firmly established that BCG can do this effectively and with a minimum risk, it follows that BCG vaccination should be used in the prophylaxis of leprosy

It has not been proved that this artificially induced positivity indicates immunity to leprosy The results of vaccinating a large number of contacts, as Souza-Campos is doing in Goyaz, Brazil, alone will establish the value of BCG in leprosy Both the Third Panamerican Conference of Leprology held in Buenos Aires in 1951 and the Madrid Congress recommended that extensive surveys of the entire population of endemic areas be made with BCG

It is further recommended that such measures as education of the public, stimulation of scientific investigation, and economic aid to the families of these patients be adopted.

In order to achieve maximum benefit from antileprosy campaigns, it is important to obtain full information about the characteristics of the disease in countries where it is endemic. Epidemiologic surveys of this kind should consider the incidence of the disease and of its different types, as well as social, economic, climatic, and racial factors.

A successful antileprosy campaign can only be conducted by paying careful attention to the following details

1. A well-run sanatorium is required for establishing the physical and mental rehabilitation of patients having contagious types of leprosy It should be situated near a large city and have a capacity of approximately 1000 beds. There should also be ample facilities for patients to engage in remunerative work.

2. Private rooms and wards should be maintained in the general hospital of the city lying close to the sanatorium, where patients may remain for observation or treatment of mildly positive or transitory types of the disease, as well as for treatment of patients with associated disorders.

3. The out-patient department, or dispensary constitutes the axis around which revolves the numerous activities of the antileprosy campaign. The function of this department embraces the treatment of ambulatory patients, the detection of new cases, the

examination of contacts, the collection of epidemiologic data, and the training of technical assistants.

It is most important, for reasons of attracting as many persons as possible without awakening their suspicion as to the true character of the dispensary to call this department "Skin Clinic."

4. A "Home" should be provided for the care and education of healthy children whose parents are undergoing active treatment in the sanatorium or general hospital.

5 It is recommended that institutes for research work be established for the study of problems relating to leprosy in all of its phases.

Until the advent of the sulfones, the sanatorium was the most important unit in the fight against leprosy since it constituted almost the only method for preventing the spread of infection in bacteriologically positive cases.

All this has been changed with the discovery of the sulfones, whereby the importance of treatment has displaced that of isolation. The dispensary thus assumes first place in the campaign against leprosy

The final elimination of this ancient scourge is not far off provided that the development of more active therapeutic agents continues at the present accelerated rate and provided that the promising results obtained with the reversal of the lepromin test from negative to positive through the action of BCG be confirmed *by future experience, thus reducing to a minimum the development of leprosy in contacts.*

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talc is indicated. Actual infection is best treated with daily injections of penicillin.

Furuncle or furunculo is a deep folliculitis associated with suppuration of the surrounding tissues, caused by Staphylococcus aureus, and resulting in tissue necrosis The complications to be feared are septicemia and lymphangiitis, although the advent of the antibiotic drugs has greatly reduced their incidence.

Carbuncle or antrax is a small group of furuncles accompanied by signs of systemic involvement. It should be differentiated from kerion and malignant pustule, the latter disorder being called car bunco in Spanish.

The most effective treatment for a "ripe" carbuncle is total sur gical enucleation. Since carbuncles often occur in diabetics over 40 years of age, it is best to avoid surgical intervention in these cases, treating conservatively instead with penicillin, a treatment that is usually adequate for smaller carbuncles which have not yet become necrotic.

Folliculitis and boils caused by exposure to greases, oils, tars pitch, waxes, and other similar substances are met with especially in persons with hairy arms and legs who work with these materials. Acneform pustules and comedones are particularly common in young workers with excessively oily secretions on the face, chest, and back.

Boils on the arms or legs may be eradicated by the application of Soft Soap U.S.P The soap is lightly ...ared on the affected extremity the first night and in larger a... on each successive night until a degree of inflammatory r... reached ... will insure satisfactory exfoliation. After ... has bee... ...d, the affected part should ... dage ... ze. ...ity of the inflammatory r... ay ... by a layer of some permeal ... l ...

As the staphyloco ... tes ... the or surrounding epid ... ect ... ency to persist and l ... s ... biotic drugs. This ... l ... or pseudopelade, fo ... or acne necrotica, ... miliaris, which wa ...

sycosis capillitii. The conjunction "or" denotes synonymy This is an antiquated mixture of Latin and English terms requiring simplification and in some instances, liquidation.

Cicatricial alopecia is marked by inflammation and atrophy of the scalp, often producing an effect that has been likened to "footsteps in the snow The staphylococcus is regarded by many as the etiologic agent, although these same authors admit that the organism has not been recovered from lesions of the disorder They explain this discrepancy in their logic by concluding that a systemic factor is present.

Lichen planus with follicular arrangement of the lesions is called lichen planopilaris. The detection of this form of lichen planus of the scalp is difficult because both clinical and histologic appearances differ from the customary The patches of alopecia are reddened, shiny atrophic, and dotted with patulous keratotic follicles which are most pronounced at the border The histologic changes in material taken from the patches are those of lichen planus, involving the follicle and perifollicular tissues in addition to the typical alterations of atrophic lichen planus consisting of an atrophic epidermis a subepidermal infiltrate consisting of fewer plasma cells than in the earlier phases of the disorder and sclerotic connective tissue. The follicles are dilated and filled with densely laminated keratotic material. In sections made from a completely atrophic patch, it is seen that the follicle has become obliterated due to the pressure of the surrounding infiltrate, which resulted in shutting off the blood supply to the base of the follicle.

Thus all stages of both lichen planopilaris and cicatricial alopecia are marked by similar clinical and histologic appearances, a similarity which arouses suspicion that the latter disorder is possibly a "burned out" lichen planopilaris. It seems reasonable to assume that an intimate connection exists between all the clinical forms of lichen planus and that Little s syndrome and cicatricial alopecia are merely varieties of localization or evolutionary stages of the disorder

When suppuration is added to cicatricial alopecia, the resulting condition approximates folliculitis decalvans, a conception by no means universally accepted, many writers maintaining that the

talc is indicated. Actual infection is best treated with daily injections of penicillin.

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As the staphylococcus penetrates deeper into the hair follicle or surrounding epidermis the infection shows an increasing tendency to persist and leave scars, in spite of treatment with the antibiotic drugs. This group of disorders includes cicatricial alopecia or pseudopelade, folliculitis or acne decalvans acne varioliformis or acne necrotica, and pustular perifolliculitis or acne necrotica miliaris which was originally described by Rayer and named

The stiff hairs within the nose are sometimes the site of a localized folliculitis which occasionally perforates the skin and produces a pustule on the nose containing a hair constituting the condition called perforating folliculitis of the nose.

The sycosiform infections of the face, neck, and body are involved in a nomenclatural chaos. Keloidal folliculitis, for example, is a better term than dermatitis papillaris capillitii or acne keloid because it implies just what it is—an infection of the hair follicle resulting in keloidal formation. Most patients having this disorder are short necked men, the friction of the shirt or coat collar rubbing the staphyloccus into the follicle.

Coccogenous sycosis, which usually begins on the upper lip following an attack of rhinitis or common cold, is a chronic, scarring form of pustular folliculitis of the hairs of the bearded region. Its frequent resistance to treatment rests on an anatomic circumstance, the staphyloccus breaking through the hair sheath to invade the epidermis where it is walled off inside a microscopic abscess, safe from blood-borne antibiotics and topical applications.

Another factor to be considered is sensitization to the nasal drip in patients with persistent nasal catarrh. It is therefore essential to clear up this condition before going on to treat the infected hairs.

A treatment promising a fair measure of success is the application of the much neglected solution of sulfurated lime U.S.P to the affected areas. The solution is soaked on gauze in the strength of two teaspoonfuls to a glass of water and it must be applied hot. This is followed by the manual epilation of all visibly infected hairs, after which a lotion containing an antibiotic drug is daubed on.

It is strange that a common disorder like ingrown hairs has received such scant attention by dermatologists. Although the appearance of ingrown hairs at first glance resembles coccogenous sycosis, a close inspection reveals an entirely different condition.

The picture is composed of pinhead sized, skin-colored or red papules and pustules scattered throughout the bearded region but not connected with the hair follicles. The hairs cannot be grasped with tweezers because they either grow directly under

and parallel to the epidermis or they emerge from the skin to describe an arc with the point of the hair boring into the skin where a pustule often forms, unconnected with the opening of a follicle, thus forming a false folliculitis that gives rise to a foreign body reaction. In examining serial sections of the skin from such areas I found that many of the hair shafts described a curve extending from deep in the dermis to near the surface and in such an oblique manner that the hair apparently did not possess enough strength to overcome the adverse component of force, instead contenting itself with crawling along under the horny layer No spiral hairs or cysts, such as occur on the neck where the collar rubs, were found in these individuals.

A contributory cause appears to be the irregular and chaotic direction of the hair lines. Normally the hairs in this area spread out fanwise up and over each side of the face from a point on the neck midway between the chin and the ear In this condition this pattern of hair lines is violently disturbed, resulting in a haphazard arrangement of hair growth. The anomaly is found in men of all nations but especially in those of mixed races.

Craig ascribes the formation of infected and ingrown hairs to shaving against the grain and other faulty shaving procedures. In my article published in 1926, I stated that repeated insults due to shaving may aggravate but not cause the condition. My conclusions were based on the result of serial histologic sections which showed that many of the hair shafts in my patients described a greater curve extending from deep in the dermis to near the surface of the skin than in normal controls.

My patients were of mixed races and had noticed the condition in early adolescence before they began to shave.

In addition to the excessive curve of the hair shaft, these patients showed a disturbed direction of the hair lines, as described previously At the time, I agreed with Bolk that true ingrown hairs such as I described are found predominantly in men of mixed races. Two years later Weninger also reported the condition as an inborn anomaly of hair growth and advised his patients to grow a beard.

The only effective treatment is manual epilation of ... and ingrown hairs. This should be preceded ... tion of warm compresses and an antibiotic dressing.

Controversy exists over the cause of a group of ... atrophies occurring on the sides of the face in ... adults. The members of this group are ... ponderous names as atrophoderma vermiculatum, ulerythema reticulata, atrophia maculosa varioliformis, follicularis keratosis. All of these disorders are ... the presence of aggregations of comedones ... later develop pitted atrophic marks arranged ... pattern and by complete ignorance as to their ... some who maintain that these disorders are ... dystrophies and others that they are caused by ...

Lupoid sycosis or ulerythema sycosiforme ... pustular folliculitis caused by the staphylococcus ... from simple sycosis by being limited to a ... shows a tendency to peripheral extension ... Pus formation is minimal and limited to the ...

Infection of the skin of the trunk and ... staphylococcus often results in the formation ... exhibiting papules and pustules on an ... leaves centrally depressed areas and loss of hair ... occurs in hairy regions, as in facial lupoid sycosis.

The suppurative form of acrodermatitis con... repens usually begins as a single pustule on ... finger or toe, where it develops in a small ... duced by injury or concomitant dermatitis. ... ance on portions of the body other than the ... been reported on several occasions. The pust... is superficial, soon rupturing to disclose a ... surrounded by a collar of overhanging epide... collection of seropurulent material forms, ... area by undermining its border. In this w... extend, involving not only the entire extre... tion of the body, in which case it generally te... of the skin and ankylosis of the interdig...

staphylococcus and Pseudomonas aeruginosa have been irregularly isolated from the elements of the localized form of this disorder

Generalized acrodermatitis continua is currently regarded as identical with so-called generalized pustular psoriasis, which is a misnomer since it has nothing to do with psoriasis. Histologically acrodermatitis continua is characterized by the presence of the spongiform pustule of Kogoj occurring in the upper layers of the rete malpighii.

In the localized form of the disease, a good procedure is to cut away the overhanging border of skin with scissors, being certain to remove it entirely even at the expense of some healthy tissue. This is followed by the daily application of a 10 per cent aqueous solution of silver nitrate to each infected area in conjunction with the pressure application of the water-cooled ultraviolet light for two to four minutes. This is repeated on successive days until fresh pustules and moisture no longer form. A preparation containing a wide spectrum antibiotic is rubbed energetically into the infected areas, and a dressing is applied.

The occurrence of deep-seated pustules located on a shiny dry red skin and limited to the palms and soles has given rise to a confusion of names. It was called pustular psoriasis of the palms and soles by Barber pustular bacterid by Andrews, and acrodermatitis pustulosa perstans by Sachs. Lever's suggestion of the term pustulosis palmaris et plantaris is a good one. All that can safely be said about this recalcitrant eruption is that it is an entity without any relation to psoriasis and that its cause is unknown.

Acne conglobata is characterized by the presence of cold abscesses which result in the formation of bridge-scars in regions generally spared by acne. These symptoms are also typical of dissecting cellulitis of the scalp. In this disorder fluctuant or solid nodules averaging 2 cm. in diameter and joined together with keloidal scars similar to those in acne conglobata are met with on the scalp, being especially numerous over the occipital region where many atrophic scars may be usually noted. Many nodules are connected with each other through sinus formations.

Because of this morphologic simil[illegible], it would be best to do away with the term acne conglob[illegible] not acne at all, call-

ing the disorder dissecting cellulitis of the body to indicate its identity with the disorder occurring on the scalp, which was described by Hoffmann.

The treatment of dissecting cellulitis of the scalp or body is primarily surgical, wide exposure of the subcutaneous tissues and sinus tracts with evacuation of pus from the lesions being required. The systemic use of penicillin and the local use of a wide spectrum antibiotic ointment in conjunction with surgical intervention are indicated.

Originally represented by Hallopeau as an independent disease, dermatitis vegetans is currently regarded as a complication of a preceding pyoderma of either staphylococcal or streptococcal origin. The process begins with the development, singly or in groups, of miliary papules and pustules that later go on to form lichenoid and vegetating elements These exuberantly growing papules resemble such various diseases as blastomycosis, verrucous tuberculosis, bromoderma, syphilis, epithelioma, and other disorders. I observed an instance of this complication in a patient at Quiroga's clinic, the infant showing four or five soft, fungating swellings on the scalp, each of which was about 2 cm. in diameter Pus could easily be expressed from the nodules, and they readily yielded staphylococci. The histologic picture was consistent with that originally described by de Truffi. A clinical resemblance to bromoderma was marked and as if to emphasize this difficulty in diagnosis, it was subsequently established that the mother had been taking bromides.

Dermatitis vegetans of this type not infrequently resembles leishmaniasis or sporotrichosis in Central America. The similarity of dermatitis vegetans to leishmaniasis is especially marked in patients with the lupoid variety of leishmaniasis. Streptococcal dermatitis vegetans resembling verrucous tuberculosis of the skin and chromoblastomycosis is not unusual in this area.

It is my experience in Costa Rica that there is a good deal more to the treatment of this condition than the administration of antibiotic agents. Although the response to these agents is usually prompt and effective, recurrences of the disorder occur with embarrassing frequency When, however the use of the antibiotics is supplemented with local treatment consisting of

solutions of potassium permanganate or copper sulfate, the incidence of permanent cure rises perceptibly

Pyoderma gangrenosum is synonymous with dermatitis gangrenosa, chronic undermining burrowing ulcer and microaerophilic hemolytic streptococcus infection. The disorder begins with furuncular lesions that rapidly break down to form ulcers with swollen, red, and undermined borders, from which hemolytic staphylococci and streptococci have been recovered. A difficult technique is required to isolate the organism, true anaerobic conditions not being an easy matter to produce.

The condition is occasionally found following an operation for suppurative appendicitis as well as in association with ulcerative colitis. Card observed such signs of vitamin deficiency as crazy pavement skin, follicular hyperkeratoses, and a sore smooth tongue in many of his patients.

Treatment with the antibiotics is ineffective. The use of fresh zinc peroxide is recommended.

The etiologic role of the staphylococcus or streptococcus in the causation of other gangrenous processes of the skin is doubtful. A rare form of this type of disorder is granuloma gangraenescens, a report of which was made by Pardo-Castello Leon-Blanco, and Rivera del Sol. The disease begins with necrotic ulcerations in the nasal septum, and it ends fatally with destruction of the central portion of the face, leaving a large cavity

The treatment of staphylococcal paronychia with penicillin, x rays, and topical applications leaves much to be desired. The surest method for relieving the pain and terminating a pyogenic paronychia is to cut with scissors a small opening in the base of the nail where suppuration is detected. The pain is instantly relieved when the pus is evacuated. A few drops of penicillin solution are then injected into the area of incision, and a small drain is inserted.

Impetigo, exfoliative dermatitis of the newborn, ecthyma, cutaneous gangrene, pyogenic granuloma, hidradenitis suppurativa, and bacterial dermatitis are disorders of decreasing frequency and severity due to the prevalent use of the antibiotics Certain features of impetigo however still merit consideration.

A form of impetigo occasionally met with in children consists of irregularly outlined patches of lightly crusted elements appear

ing in a symmetrical pattern chiefly on the trunk and extremities. The resemblance to classic impetigo is so striking that many writers consider it a variant of that disorder although the symmetrical disposition of the lesions calls for an explanation other than that the child spreads the infection by scratching himself in exactly the same places on each side of the body.

The occurrence of stomatitis and acute glomerulonephritis during an attack of impetigo is not infrequently encountered in children in Costa Rica.

Two forms of impetigo deserving special consideration are so-called furfuraceous impetigo and tropical impetigo. Both disorders are improperly named, for the former is not true impetigo, and the latter is not confined to the tropics. So-called furfuraceous impetigo occurs chiefly in children living in tropical countries and is characterized by the presence of lightly scaling and more or less sharply defined, whitish lesions of varying size and shape. The lesions are commonly of pyogenic origin, resembling those due to fungi. Frequent after-effects of this superficial infection are whitish or grayish, depigmented areas which are known as sun-children in Spanish America. A closer acquaintance with soap would probably prevent most infections of this kind.

Tropical impetigo, although common in the tropics, is frequently encountered during a hot, humid summer in northern latitudes. It is marked by the presence of bullae and pustules chiefly in the axillae and groin. The burning sensation and the refractiveness to treatment which characterize tropical impetigo make it a particularly distressing disease. The disinfection of clothing, towels, and bed linen in conjunction with the systemic and local use of the antibiotic drugs often fails to check the infection, but a change of residence to a cool, dry climate promptly terminates it, as it does miliaria rubra, intertrigo, and other conditions induced by high humidity and high atmospheric temperature.

Perleche or boquera, regardless of whether it is caused by the streptococcus, malocclusion caused by faulty dentures, or riboflavin deficiency is a difficult condition to eradicate. Riboflavin therapy in my experience, has been a failure. At times I have had success with the local application of 10 per cent suspension of tannic acid in glycerine.

Intertrigo is usually caused by the streptococcus. Occurring behind the ears, it is often associated with matting together of the scalp hairs and reddening of the skin, which makes it resemble asbestoslike tinea. Between the toes it mimics fungous infection in a surprisingly large number of instances. The presence of pain and a violaceous tint in an interdigital area should suggest streptococcal infection. This observation was brought home to me by the frequency with which intertriginous infections are found in patients with thromboangitis obliterans.

Acute attacks of lymphangitis usually in the skin of the legs, with enlargement of the regional lymph nodes and signs of systemic involvement, are of common occurrence in the tropics. The streptococcus enters through lesions caused by fungi, chigoes, or any one of countless injuries that befall a barefooted person. When repeated attacks of lymphangitis occur each with thickening of the skin, the resulting condition is easily confused with filarial elephantiasis.

Pyogenic or bacterial dermatitis or dermoepidermitis microbiana is a frequent complication of infected wounds, insect bites, furuncles, cellulitis, *otitis media*, and similar infections It is most common in persons with varicose veins and peripheral vasculitis, in whom it occurs as the result of scratching or a slight injury The lesions are generally follicular pustules but they may assume such polymorphous forms as weeping, crusted dermatitis dry psoriasiform patches, or ulcers, the latter appearing especially in debilitated persons. Erysipelas or cellulitis is a frequent complication.

Dermatitis nodularis necrotica is characterized by a polymorphous eruption consisting of papules, pustules, nodules, and ulcers many of which are hemorrhagic. The gummatous nodules exude abundant pus before they break down and ulcerate. The entire process beginning with the initial lesion and ending with necrosis takes only two or three days. The disease does not affect the general health. Although the causative agent has not been established, the histopathologic evidence at hand seems to indicate that the disease represents a vascular reaction of hypersensitivity to infection, particularly streptococcal or tuberculous.

The histoanatomic changes support this concept. They consist mainly of proliferative changes of the walls of the small arteries and arterioles particularly of the intima, with obstruction of the lumen. In addition, one sees focal areas of red blood cells and polymorphonuclear leukocytes throughout the dermis, with a dense infiltrate of lymphocytes and plasma cells around the blood vessels These findings simulate those of necrotizing arteritis, especially of the early and moderately advanced phases of periarteritis nodosa.

The treatment of the foregoing disorders with the systemic use of penicillin and the local application of ointments of the wide spectrum antibiotic drugs greatly reduces their incidence wherever these drugs are available. Their prohibitive cost in many Latin American countries and their unavailability in the jungles, virgin forests, and other areas of difficult access in these lands create a situation with which physicians will have to contend for some time to come.

The incidence of pyogenic disorders would be greatly reduced in countries where the cost of the antibiotic drugs is high, if good soap were available at a price that everyone could pay This would put an end to ineffective cleansing with wood ashes and alkaline fruit juices.

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21

Miscellaneous Bacterial Diseases with Cutaneous Manifestations

By

Frederick R. Schmidt

Pseudomonas aeruginosa. This is a slender gram-negative rod like organism with a characteristic odor The species Pseudomonas pyocynea elaborates a deep blue pigment called pyocyanin, while other species produce a yellowish green pigment termed fluorescein, which is capable of fluorescence when exposed to filtered ultraviolet radiation.

As a cause of infection of the external ear canal and auditory meatus, Ps. aeruginosa is presently conceded priority over other pyogens and fungi. Its presence as a secondary invader in chronic ulcers of the skin and generalized bullous eruptions has been noted, and several instances of localized acrodermatitis continua caused by this organism have been reported.

The topical application of Polymyxin B or neomycin sulfate is good treatment in infections of the external ear canal due to this organism

Brucella dermatitis. Wherever goat cheese and milk from cows or goats are consumed fresh and raw the possibility of infection with Brucella melitensis, variety abortus, exists. The incidence of brucellosis is therefore high in Northern Mexico and Chile, in contrast with a low rate in tropical countries where it is an old custom to boil the milk to prevent spoilage.

Various kinds of eruptions have been reported as associated with this disease, such as urticarial, purpuric, scarlatiniform, and morbilliform varieties. When the lesions are those of dermatitis they are characterized by discrete follicular papules and pustules

Eruptions of this nature are infrequent manifestations of the infection In two instances of the disorder which I observed and

in those reported in the literature, the organism could not be demonstrated, which suggests a hypersensitivity factor in their production.

The only convincing proof of brucellosis is the isolation of the causative organism. Other procedures, such as the agglutination test and blood culture are merely confirmatory

The use of chlortetracyclone in doses of 2 gm. daily for 7 to 21 days is usually effective in acute brucellosis It has little effect on the course of chronic brucellosis.

Keratosis blennorrhagica, Reiter s disease, and psoriasis with arthropathy occasionally engage our attention because of the clinical and histologic resemblance they bear to each other

Keratosis blennorrhagica. The skin in this condition is widely affected by an eruption of a bizarre nature, and almost the entire surface of the body is covered with numerous crusts placed at ir regular intervals from each other On close inspection, these crusts reveal themselves as yellow horny and small projections when they are on the head, being larger and darker when on the feet. Many of the excrescences are surrounded by a zone of red ness. The palmar and plantar surfaces are often carapaced with masses of horny elements that peel off layer after layer the right hand being most heavily affected. The crusts may so heavily cover the fingers that they seem to pry the nails from their beds. The lesions only rarely yield the gonococcus.

In milder instances of the disorder the initial papules and pustules are generally confined to the palms and soles, where they slowly fuse during a period of several weeks to form masses of horny elevations.

Reiter s disease. This disorder is characterized by an urethral discharge, arthritis, conjunctivitis, and by the occasional presence on the skin of sterile vesicles late in the course of the infection. This combination of symptoms closely resembles that in kera tosis blennorrhagica, where vesicles rather than pustules are some times the first signs of the disorder Although gonococci have been demonstrated on rare occasions in the cutaneous elements of gonorrheal keratosis, the causative agent of Reiter s disease is unknown. Treatment with antibiotics has no effect.

The distinction of these two affections from each other and

from psoriasis with arthropathy is sometimes difficult. Neither the history nor the clinical or histologic picture of any one of these diseases is sufficiently defined always to permit its differentiation.

The joints are involved in all three conditions, but here again a clear separation on a basis of articular symptoms cannot always be made. Experience indicates that gonorrheal infection shows a predilection for large joints, such as those of the knees and ankles, while psoriasis affects the small ones of the hands and feet, especially those of the distal interphalangeal articulations. This pattern, however cannot be relied upon as a basis for differentiation because the findings on x ray examination of the joints are usually quite similar in corresponding phases of these diseases.

Focal infection is considered by many as a precipitating factor in the production of psoriasis with arthropathy My experience, however does not bear out this contention, as the removal of tonsils and infected teeth as well as the making of windows in sinuses caused no improvement other than temporary

Tularemia. The causative agent of tularemia is Pasteurella tularensis, which is carried from one rodent to another by ticks and various insects, the jack rabbit being the chief source of infection in the United States. The deer fly and Argasid tick are the principal transmitters of the organism from the rabbit to man.

The ulcer which forms at the site of inoculation has a punched-out appearance. The regional lymph nodes become enlarged, and nodules form along the lymphatics. The nodules usually soften and form ulcers The rash appears some 14 days later and consists of erythema, urticopapules and pustules.

The diagnosis is established by the outcome of the agglutination test which, when positive, becomes so in the second or third week.

Anthrax or carbunco. This is a disease chiefly of herbivorous animals, especially cattle. The Spanish word "antrax" is easily confused with the English word "anthrax." The Spanish word designates a carbuncle or a small group of furuncles whereas the English word is used for the infection caused by the bacillus of anthrax.

The initial lesion is a red maculopapule soon developing into a vesicle at times becoming hemorrhagic, and usually terminat

ing in a malignant appearing carbuncle. Lloyd showed that animal products such as wool, hair hides, and skins have become increasingly important as an industrial hazard and that imported wool, used in the making of carpets, alone is responsible for the majority of cases of industrial anthrax in the United States. In agricultural anthrax, an immediate and strict quarantine should be placed about the infected area, a necessary measure to prevent the dissemination of anthrax spores, which are capable of surviving in the soil for years.

Streptomycin and neomycin are the drugs of choice in the treatment of anthrax.

Behcet's syndrome. This condition does not properly belong in this section, since its bacterial origin is doubtful. However, in genital lesions associated with this disease, B crassus has occasionally been isolated. This occurred in a patient of mine, a woman aged 24, who had two painful ulcers of the vulva, aphthous lesions of the mouth, inflammatory lesions of the eyes, and erythema nodosumlike elements on the legs. In some cases, there are coexistent symptoms referable to the gastrointestinal tract, central nervous system, and joints. The disease is variously attributed to hypersensitivity or to virus. Treatment is unsatisfactory

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Treatment of Syphilis

By
Miguel Angel Mazzini

THE TREATMENT of syphilis is conditioned by the chronic and erratic nature of its course

The use of modern therapeutic agents is effective in curing 100 per cent of patients with primary syphilis. In advanced stages, with irreversible structural changes, it is usually possible to retard the process and thereby greatly prolong the patient's life Patients having neurosyphilis can usually be returned to their normal activities.

The effectiveness of modern therapy particularly in the primary stage, is attested by the frequency of reinfection, infrequency of tertiary lesions, scarcity of central nervous system involvement, and rarity of congenital syphilis.

The management of primary syphilis in young subjects is a relatively simple matter for they are not as a rule burdened with other diseases capable of lowering the threshold of tolerance to antisyphilitic agents. The presence of other coexistent organic disease or irreversible structural changes due to the syphilitic process makes the treatment of visceral syphilis more difficult, since injudicious therapy can lead to serious damage.

The following treatment plan should be modified or altered whenever this becomes advisable in the judgment of the attending physician

PRIMARY ACQUIRED SYPHILIS

The combination of penicillin and bismuth is the best available treatment for seronegative and seropositive primary syphilis.

Penicillin acts by immobilizing treponema pallidum through

neutralization of the enzymes participating in the catabolism of deoxyribose nucleic acid. It also interferes in the catalytic systems of respiratory enzymes and of those concerned with the transport of hydrogen.

Bismuth exerts its influence on the parasite by interfering in the regulation of succinic and pyruvate oxidase. Furthermore, by blocking out the -SH groups, it inhibits the formation of cystein and glutamic acid which are essential to cellular respiration of the parasite.

The following treatment plan will preserve seronegativity in seronegative primary syphilis and rapidly reduce the titer to zero in seropositive primary syphilis. In order to avoid visceral involvement, treatment should be energetic, and the total dosage should be given within a short period of time.

The treatment consists of two series of penicillin and bismuth, punctuated by a rest period of four weeks between series. The duration of this treatment plan is 24 weeks

Penicillin is employed in the form of procaine penicillin in aqueous suspension (PP) or in the form of procaine penicillin in oil fortified with 2 per cent aluminum monostearate (PAM) If PP is used, 500 000 units are administered intramuscularly each day for 15 days, with a total dose of 7,500,000 units If PAM is used, 600 000 units are given every 48 hours until 4,800 000 units have been administered. Liposoluble bismuth is given concomitantly every three days in doses of 0 07 gm. of metallic bismuth until a total dosage of 1.4 gm. is reached. The duration of this series is 10 weeks.

If the patient gives a history of an allergic background, it is advisable for him to take an antihistaminic tablet before each injection of penicillin.

A rest period of four weeks is now interposed, during which time oral vitamin C and injectable liver extract are given in order to prevent the occurrence of such side-effects of bismuth as gingivitis asthenia, and rheumatic pains. A blood test and urinalysis should be made at the end of this period.

The second series of injections consists entirely of liposoluble bismuth in doses similar to those employed in the first series until 1.4 gm of metallic bismuth have been given.

This treatment almost always brings about involution of lesions and seronegativity in subjects initially having a positive blood test. If the blood test is negative at this time, further treatment is suspended. Clinical and serologic examinations are then made every six months for two years, and a lumbar puncture is performed two years after the last series of bismuth injections.

The serologic titer provides an accurate index of the efficacy of treatment, and should be determined at frequent intervals.

SUMMARY OF TREATMENT OF PRIMARY SYPHILIS

First series (10 weeks)	Penicillin *and*	PP 7,500,000 U., or PAM 4,800 000 U
	Soluble bismuth	1 4 gm. of metallic bismuth
	Rest period of 4 weeks	
Second series (10 weeks)	Soluble bismuth	1 4 gm. of metallic bismuth

SECONDARY ACQUIRED SYPHILIS

The treatment depends on whether we are dealing with early or late secondary syphilis. The prognosis in early secondary syphilis is good in respect to clinical and serologic symptoms although elimination of all foci of spirochetes can not always be accomplished.

The cutaneous and mucosal lesions such as roseola and erosive syphilid, usually disappear in a few days the papular lesions usually taking a longer time. The blood test generally becomes negative after the first series of injections.

SUMMARY OF TREATMENT PLAN OF EARLY SECONDARY SYPHILIS

First series (10 weeks)	Penicillin *and*	PP 7,500,000 U., or PAM 4,800,000 U
	Soluble bismuth	1.4 gm. of metallic bismuth
	Rest period of 4 weeks	
Second series (10 weeks)	Similar to first series Rest period of 4 weeks	
Third series (8 weeks)	Soluble bismuth	1 12 gm. of metallic bismuth

Duration of Treatment—36 weeks

Late secondary syphilis is characterized by solitary lesions of the skin and mucous membranes which tend to form incomplete rings or groups of lesions They arise from 6 to 12 months or more after the appearance of the chancre and are resistant to treatment. The serologic symptoms disappear with difficulty

The treatment plan should be altered in the presence of complications or failure of the patient to respond satisfactorily the serologic titer being an index of the greatest value in this stage of syphilis. The suggested four series of injections may at the discretion of the physician, be raised to six.

SUMMARY OF TREATMENT PLAN OF LATE SECONDARY SYPHILIS

First series (10 weeks)	Penicillin *and*	PP 7,500,000 U., *or* PAM 4,500,000 U
	Soluble bismuth	1.4 gm. of metallic bismuth
	Rest period of 4 weeks	
Second series (10 weeks)	Similar to first series Rest period of 4 weeks	
Third series (8 weeks)	Soluble bismuth Rest period of 4 to 6 weeks	1.18 gm. of metallic bismuth
Fourth series (8 weeks)	Insoluble bismuth	1.2 gm. of metallic bismuth
	Duration of Treatment 48 to 50 weeks	

It will be noted that insoluble bismuth is used in the fourth series. The form employed in my practice is bismuth subsalicylate, one ampoule of which contains 0.075 gm. of metallic bismuth. Injections are given every three days.

Two more series of insoluble bismuth injections should be given if the results are not satisfactory after completion of the fourth series, interposing a rest period of six weeks between the two additional series.

Following a satisfactory response to treatment, the patient should return for observation every six months for two years. If examination of the spinal fluid, circulatory system, and ocular fundus fails to reveal abnormalities at these times, the patient may be pronounced clinically cured.

In cases of clinical or serologic relapse, treatment should be instituted at once The type of treatment will depend on the symptoms exhibited by the patient.

The prognosis depends on the presence or absence of visceral involvement. Since this is not always easy to determine, the *prognosis in late secondary syphilis should be guarded.*

MUCOCUTANEOUS TERTIARY SYPHILIS

The prognosis of this form of acquired syphilis is dubious, the best that can be hoped for from treatment being the clearing of the lesions and the arrest of the infectious process. Seronegativity is difficult to obtain. Persistence of positivity in the presence of clinical cure and negative spinal fluid findings does not imply failure of treatment. Nevertheless it is difficult to convince patients of this

A thorough physical and laboratory examination should be made before beginning treatment in order to rule out coexistent nonsyphilitic visceral disease as well as asymptomatic syphilitic involvement of the viscera. It is advisable to place the patient on oral potassium iodide therapy before instituting more active treatment. Three grams daily of potassium iodide should be given for 10 days.

Four *series* of *penicillin* and bismuth are then given over a period of 48 weeks. The first series consists of 600 000 units of PAM every 48 hours until a total of 4,800 000 units are reached and simultaneously 1 cm. of bismuth subsalicylate every three days for nine weeks making a total of 1.35 gm. of metallic bismuth. In patients with an allergic background it is advisable to begin this series with bismuth for two weeks before starting the penicillin.

A rest period of four weeks is interposed between each of the four series of injections during which time a blood test and urinalysis are made

The second series is similar to the first, except that soluble bismuth is substituted for the insoluble form In the third series, a return to insoluble bismuth is made, penicillin being employed in the same dosage as in the first two series. The fourth series is similar to the third.

The further conduct of the physician in charge depends on the outcome of the examination made at the end of the 48 weeks of treatment. If the patient shows complete clearing of lesions, a negative blood test, and normal spinal fluid findings, he may be discharged, subject to regular observation. If, however the results of treatment are not satisfactory additional bismuth injections totalling 2.7 gm. may be given. Abnormal spinal fluid findings persisting after the termination of additional bismuth injections are a clear indication that the patient should henceforth be treated for neurosyphilis.

Patients showing negative blood tests, absence of symptoms throughout two years of trimonthly examinations, and normal spinal fluid and ocular findings may be discharged as cured.

The prognosis depends on the amount of destruction caused by the treponema before the institution of effective treatment and on the age of the patient. Tissue depletion occasioned by age or by irregular habits of living is an important factor in foretelling the future course of the disease.

VISCERAL SYPHILIS

Cardiovascular syphilis represents the commonest form of late syphilis It occurs in subjects who have either been insufficiently treated or not treated at all. The aorta and its valves and the large blood vessels are most commonly affected, involvement of the myocardium being usually secondary to that of the aorta.

The presence of cardiac insufficiency seriously complicates treatment. Furthermore, there is always a great risk of harming the patient, since overactive treatment can bring on episodes of ventricular fibrillation and Jarisch-Herxheimer reactions

The treatment plan for cardiovascular syphilis is necessarily sketchy in character since each case must be individualized. With this in mind I would like to present the following schedule

1. Oral potassium iodide therapy for 10 to 15 days, depending on the degree of tolerance to iodides. The dose of the drug is 3 gm. daily

2. Bismuth subsalicylate in doses previously indicated or quinine iodobismuthate in doses of 3 cm. every three days for eight weeks.

Before beginning treatment, the patient should undergo a thorough physical examination. Patients with paresis are generally advanced in years and consequently show enough degenerative changes to put us on our guard against the possibility of treatment accidents due to these senile changes.

The management of a patient with paresis is always difficult and should only be undertaken with the active assistance of a psychiatrist. *His advice should be taken in respect to the possible* use of artificial hyperthermia or shock therapy Regardless of whether or not fever therapy is employed, penicillin is given as PAM in doses of 1,200 000 units every 48 or 72 hours until a total dosage of 12,000 000 units has been administered.

In my experience the results obtained with the combination of penicillin and fever therapy are in no way superior to those obtained with penicillin alone.

A rest period of three months is allowed the patient, after which a series of injections similar to the first series is given. This is followed with an interval of three months, after which the further conduct of the case depends on whether or not the patient has shown clinical improvement. If improvement has taken place, an examination of the spinal fluid is made, and in the event that the findings indicate improvement, recourse to shock therapy is highly effective Further treatment of these patients with penicillin and shock therapy generally brings about sufficient mental improvement to allow them to return to normal life.

If however the results of treatment up to this point are unfavorable it is best to consign the patient to a psychiatrist, since further treatment along the lines indicated is ineffective.

Tabes dorsalis should be treated in general like paresis The prognosis is more favorable than in paresis providing that the disease is not of excessive duration. It will be recalled that treatment usually does not abolish the pupillary reflexes or the episodes of gastric crisis, nor does it restore sexual potency and the sensation of deep pressure.

A favorable prognosis may be entertained in patients showing a reduction in the cell count of the spinal fluid after one year of treatment. The disease becomes stabilized and there is a good chance that the lightning pains and gastric crisis will be greatly alleviated.

Primary optic atrophy is best treated with penicillin and fever therapy The injections of penicillin are given according to the schedule for general paresis Hyperthermia is induced by eight or 10 injections of malarial blood of the benign tertiary type.

The prognosis is unfavorable because, even with treatment, blindness may occur

TREATMENT OF CONGENITAL SYPHILIS

Because of the efficacy of penicillin in the treatment of the pregnant syphilitic woman, congenital syphilis can almost entirely be prevented by prenatal therapy It is suggested that the treatment consist of 500 000 units of penicillin daily for 20 days, with a total dosage of 10,000 000 units, this to be given in conjunction with biweekly injections of 0 07 gm. of liposoluble bismuth until 20 injections have been given.

If the mother has not received treatment during her pregnancy the infection will usually assume one of the following forms

1 Early congenital syphilis (from birth to the third month) It is suggested that the child presenting signs or symptoms of early congenital syphilis be given 400 000 units of penicillin per kilogram of weight daily this amount to be divided over 15 days. I have found it advantageous to use solvents capable of slowing the absorption of the penicillin or N N dibenzylethylenediamine dipenicillin G This treatment is combined with 15 biweekly injections of either liposoluble bismuth or bismuth subsalicylate, each injection to contain 3 mg of metallic bismuth per kilogram of weight.

A rest period of four weeks is now allowed, after which a second series of bismuth injections is given, similar to the first series. If the attending physician finds it advisable a third series of bismuth injections is then given after a rest period of four weeks.

If the blood test is negative after the first series, serologic control should be made every six months for two years. If the laboratory and clinical examinations prove normal at the end of two years, the child may be considered cured.

2. Late congenital syphilis (after the second year of life) The suggested treatment plan for children with this form of congenital syphilis is similar to that for adults with tertiary acquired syphilis. The results in children, however are much less satisfactory In-

terstitial keratitis is the most recalcitrant symptom and requires the following specialized form of treatment

a) Penicillin G in series totalling 10,000,000 units.
b) Cortisone in the form of a collyrium and tablets for oral administration, providing that the infection is in an early congestive phase.
c) Fever therapy
d) Vitamin B

If there is a coexistent tuberculous infection, use should be made of isoniazid, para aminosalicylic acid, streptomycin, and vitamin D_2

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23

Yaws (Framboesia Tropica)

By

Tancredo A. Furtado

Definition. Yaws is a contagious, infectious, and nonvenereal treponematosis of tropical and subtropical regions which produces specific cutaneous and osseous manifestations. It is not hereditary it rarely affects the mucous membranes and never produces visceral, ocular or nervous symptoms similar to those of syphilis.

Etiology The causative agent, Treponema pertenue, is morphologically indistinguishable from T pallidum. According to Yasuyama, T pertenue survives outside the organism for only 30 minutes in physiologic saline solution and two hours in human serum. This low vitality contrasts with that of T pallidum which, according to Harrison, survives for 50 to 84 days and maintains its vitality for six days at 37 C. Inoculation of monkeys and rabbits with the two spirochetes always causes clinically and histologically different lesions. According to Turner Turner and Chesney Ferris and Turner and MacLeod and Turner this should be attributed to the inherent biologic characteristics of each of these organisms.

Epidemiology Occurring exclusively in tropical and subtropical lowlands where the rainfall is great, the soil damp, the vegetation abundant, and living conditions and clothing are primitive, yaws occurs in endemic foci in contrast with the universal occurrence of syphilis. A large number of arthropods may act as mechanical vectors, among which are Hippelates pallipes (the commonest) Musca domestica, Ornithodorus talaje, Amblyoma cayenense, and some bloodsucking insects.

Symptomatology The course of yaws may appropriately be divided into early and late stages, adding a latent stage to in-

clude asymptomatic forms of the infection. Any attempt to classify yaws is purely arbitrary however because of frequent overlapping of the primary and the secondary manifestations, although overlapping of early lesions with those of the late stages has never been convincingly demonstrated. Furthermore, the primary lesion may outlast the secondary lesions. It is also possible for a primary lesion which is caused by an injury and which is associated with infection to ulcerate and become progressively transformed *in situ* into an ulceration of the late stage, particularly in persons in whom the absence of a generalized eruption prevented the development of immunity

The causative agent penetrates the organism through a solution of continuity of the skin which at times is not visible but more frequently is represented by cuts, wounds, abrasions, or pre-existing dermatoses. The primary lesion appears as a large, round, crust-covered, fungating papule measuring from 2 to 6 cm. in diameter after an incubation period which varies between ten days and six weeks. When the crust is removed, a moist, whitish, or pinkish, mammillated surface resembling a raspberry is exposed. In rare instances, the primary lesion is a small papule, a scaling macule, or an ulceration. Such lesions are usually single and in about 80 per cent of cases are situated on the lower leg below the knee. Multiple lesions result from the simultaneous inoculation of the infection in several different areas.

The duration of the primary lesion is extremely variable. It may involute before the stage of generalization, or it may persist and coexist with the secondary lesions, or it may even outlast them. The type of rupture of the skin, the number and virulence of the causative agent, the reaction of the organism to the infection and pre-existing or superimposed infection are all factors capable of influencing the morphology and evolution of the primary lesion.

The spread of the infection to the lymphatics takes place at an early stage which explains the occurrence of satellite lesions. The regional lymph nodes as well as distinct nodes become enlarged and some contain treponemas. T pertenue also invades the blood stream very early in the course of the disease as is shown by a positive serologic reaction as early as the third week of the infec-

tion. Thus the infection spreads by both the blood and lymphatic channels.

Secondary framboesiform lesions may appear at any time between the first week and fourth month of the infection. These framboesomas are vegetating, crust-covered more or less ulcerating lesions which are produced by the hematogenous spread of the infection, they are morphologically similar to but smaller than the primary lesion.

Occurring singly or in combination with these framboesomas are nonvegetating lesions called framboesids which are generally regarded as resulting from the hematogenous spread of the treponemas in a person previously sensitized by that antigen. Framboesids appear under various aspects, among which are miliary papules, roseolalike macules, lichenoid and psoriasiform plaques, and circinate lesions.

Framboesomas and framboesids may be distributed over the entire skin or confined to the following areas in order of frequency: face, extremities, buttocks, thorax, perineum, external genitalia, neck, back, and abdomen. The scalp is rarely affected. Localization on the palms and soles produces very painful inflammatory lesions which frequently incapacitate the patient for work. Rabello stresses that these lesions are altogether different from the palmar and plantar lesions of the late period.

Participation of the skeletal tissues occurs in the early stage of the disease but to a lesser degree, it being unusual to find serious bony deformities in this early stage.

The recurrence of vegetating framboesomas and nonvegetating framboesids at various intervals during the first two or three years of the infection is by no means unusual. Since Schoebl showed that there is no latent infection of the lymph nodes which might act as a reservoir of treponemas, it must be assumed that these recurrent lesions are due to superinfection or reinfection.

All forms of framboesiform lesions are rich in treponemas while framboesids have few of them. The phase of generalization of the infection is accompanied by positive serologic reactions in 100 per cent of cases.

In about 50 per cent of patients, the infection is either completely dominated by the immunizing forces developed in the

evolution of the disease, or it enters a latent phase which is only recognizable by the positive serologic reaction and by incontestable anamnestic and epidemiologic data.

The remaining 50 per cent of patients develop localized lesions of the skin and bones with marked destructive tendencies. As a general rule, the more exuberant the early manifestations the less intense will be the late ones and vice versa. How can these late lesions be explained? Chambers believes that treponemas and their products arising in latent foci or from external reinoculations create a state of altered reactivity or allergy in tissues previously sensitized by that antigen, the newly invading treponemas producing destructive lesions because of the altered reactivity of these tissues.

The late cutaneous lesions of yaws appear as wartlike nodules or ulcerations. Sometimes the ulcers resemble those found in so-called tropical ulcer and at other times they mimic those associated with deep mycotic disease.

It is often difficult to distinguish the lesions of the late stage of yaws from tertiary syphilis. As a rule, however the late lesions of yaws are more extensive, more spreading, and more destructive, the resultant deformities and scars often interfering with the lymphatic circulation and thus producing elephantiasis and conditions analogous to mossy foot and Madura foot.

Hyperkeratotic lesions of the soles and palms were present in the late stage of 25 6 per cent of my patients. These lesions are called "crab yaws" and usually cause extensive thickening of the skin with fissuring and ulceration. Keratoderma of this kind is often the only cutaneous evidence of the infection and in conjunction with a positive serologic test and anamnestic data is what makes the diagnosis possible.

I have never been able to find T pertenue in the late cutaneous lesions of yaws either by direct examination or in histologic sections, although the serologic reactions are positive in over 90 per cent of patients.

The invasion of skeletal tissues produces osteitis and periostitis leading to bony deformities and mutilations, particularly of the tibia (sabre shin) Goundou is the name given to the deformity caused by hypertrophic osteitis of the nasal bones and ascending

branch of the upper maxilla. This process may set in early in the course of the disease, but it is usually a late manifestation. There is no known explanation of the fact that goundou is very frequent on the French West African Coast and very rare in countries such as Indochina and Brazil where yaws is endemic.

I have observed the following radiologic modifications circumscribed areas of osseous rarefactions (osteolysis) osteoporosis, periostic deposits, thickening of the cortical layers, and osteosclerosis. Yaws can give rise to all the osseous lesions of syphilis except osteochondritis, but involvement of the joints is much more frequent and extensive in yaws than in syphilis.

Gangosa and juxta-articular nodes should be regarded as a syndrome produced by many diseases of which yaws is merely one. Gangosa is characterized by a progressively destructive ulceration of the soft tissues and bones of the nose, the hard palate, pharynx, and posterior pillars, producing a repugnant and monstrous condition. Gangosa may begin in the nasal vestibule, nasolabial folds, or on the upper lip and progresses inward, or it may start in the hard palate or pharynx.

Juxta-artericular nodes are generally symmetrically disposed around the joints and bony prominences, particularly the knees, elbows, hips, and ankles. They must be differentiated from the subcutaneous nodules of rheumatoid arthritis and rheumatic fever fibroma, the tophi of gout, the cysts of filariasis, onchocerciasis, and fibrotic growths of traumatic origin. The great variation in the incidence of gangosa and juxta-articular nodes in different endemic foci of yaws may possibly be due to ecologic, racial, and dietetic factors.

Histopathology In both the initial lesion and generalized framboesomas, there are marked epithelial hyperplasia and dermal inflammatory infiltrates, with a predominance of lymphocytes and plasmocytes showing a tendency to perivascular arrangement. The fundamental changes in the frambocsids are similar to those just described, except for a difference in the extent and details of the individual lesion.

In advanced lesions, there is a granulomatous infiltrate, epithelioid and giant cells being rarely present. Necrosis of the kind met with in syphilis is exceptional. I regularly observed

evolution of the disease, or it enters a latent phase which is only recognizable by the positive serologic reaction and by incontestable anamnestic and epidemiologic data.

The remaining 50 per cent of patients develop localized lesions of the skin and bones with marked destructive tendencies. As a general rule, the more exuberant the early manifestations, the less intense will be the late ones and vice versa. How can these late lesions be explained? Chambers believes that treponemas and their products arising in latent foci or from external reinoculations create a state of altered reactivity or allergy in tissues previously sensitized by that antigen, the newly-invading treponemas producing destructive lesions because of the altered reactivity of these tissues.

The late cutaneous lesions of yaws appear as wartlike nodules or ulcerations. Sometimes the ulcers resemble those found in so-called tropical ulcer and at other times they mimic those associated with deep mycotic disease.

It is often difficult to distinguish the lesions of the late stage of yaws from tertiary syphilis. As a rule, however the late lesions of yaws are more extensive, more spreading, and more destructive, the resultant deformities and scars often interfering with the lymphatic circulation and thus producing elephantiasis and conditions analogous to mossy foot and Madura foot.

Hyperkeratotic lesions of the soles and palms were present in the late stage of 25.6 per cent of my patients. These lesions are called "crab yaws" and usually cause extensive thickening of the skin with fissuring and ulceration. Keratoderma of this kind is often the only cutaneous evidence of the infection and in conjunction with a positive serologic test and anamnestic data is what makes the diagnosis possible.

I have never been able to find T pertenue in the late cutaneous lesions of yaws either by direct examination or in histologic sections, although the serologic reactions are positive in over 90 per cent of patients.

The invasion of skeletal tissues produces osteitis and periostitis leading to bony deformities and mutilations, particularly of the tibia (sabre shin) Goundou is the name given to the deformity caused by hypertrophic osteitis of the nasal bones and ascending

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Pinta

By

Francisco Marquez *and* Charles R. Rein

MAL DEL PINTO or pinta, also known by other colloquial names, is a nonvenereal, endemic treponematosis. It is characterized by the presence of cutaneous lesions associated with marked color changes, which ultimately develop partial or complete depigmentation. These color changes, which are typical, have given the disease the name.

GEOGRAPHIC DISTRIBUTION AND INCIDENCE

Pinta is a primitive, tropical disease, occurring essentially in the Western Hemisphere, which probably existed for many years before the Spanish Conquest. The disease prevails in Mexico, Colombia, Ecuador Venezuela, and Bolivia, where large regions are affected. Smaller isolated areas have been described in Cuba, Brazil, the Guianas, Guatemala, Honduras, Haiti, Dominican Republic, Argentina, Africa, and Asia.

EPIDEMIOLOGY

Distribution. Pinta has no special geographic distribution as previously believed. It can occur in areas of high as well as relatively low altitudes and is also found in isolated, small zones such as Cuba, where the incidence is low

Climate. Pinta is more prevalent in tropical zones although it is not confined entirely to them. Dry weather is usually more favorable than moist for the occurrence of the disease. Most Mexicans with the disease live in inland areas.

Mode of life. Pinta is prevalent among those of poor socioeconomic levels, usually in small villages with inadequate and

unsatisfactory sanitary conditions. These people usually live closely crowded together in small huts, the entire family frequently sleeping in a single bed. In most instances the disease occurs in those who are undernourished, ill-clad, barefooted, and unclean.

Sex and age. In our original study of pinta in Mexico, it was noted that the infection was slightly higher among females than males. This may be due to the fact that women usually remain at home and are in closer contact with the affected members of their families. Pinta is essentially a disease of infancy and child hood. In our group of 133 pinta patients, the disease occurred between the ages of 1 to 15 years in 61.6 per cent of the cases.

Race. Pinta has no predilection for any race, although it occurs more frequently in Mexican Indians. In Cuba, Brazil, and other countries, Negroes are more affected than others.

TRANSMISSION

Contact. Pinta is contracted by casual contact. Since the organism cannot penetrate uninjured skin, the usual port of entry is a minute cutaneous abrasion on the exposed portions of the body We have seen two infants infected by their mothers after having been held in their arms for long periods during the day The primary lesions developed precisely at the site where they were in close and almost continuous contact with active pinta lesions on the mother's skin.

Congenital. Unlike venereal syphilis but like yaws, pinta does not produce prenatal infections. It is only on rare occasions that instances of pinta infections have been noted in infants under six months of age.

Insects. Leon y Blanco was able to transmit the disease to a volunteer by exposing his excoriated skin to insects recently fed with material containing Treponema carateum. It has not, however been established that these insects serve as true vectors in transmitting the infection. In fact, Hippelates naturally infected with Treponema carateum never have been found. As has been conclusively demonstrated in yaws, the treponemas do not invade the salivary glands of the insect, and a cycle is not developed, therefore the only way by which the disease can be

transmitted is by the regurgitated material or excreta deposited on the skin after the insect has fed upon secretions of exposed lesions As in yaws occasional transmission of pinta by this mechanism can not be excluded, although open lesions are not present in pinta, therefore mechanical passive transmission should be exceedingly rare under the usual existing conditions.

ETIOLOGY

Bacteriology The disease is caused by Treponema carateum. Under dark field examination, the electron microscope, and the phase microscope, T carateum appears morphologically identical with the treponema of syphilis, yaws and bejel.

Animal inoculation studies have been of special interest. Turner Hollander and Shaeffer have shown that the syphilis strains, including those from Bosnia, in general produce large indurated lesions, whether inoculations are made into the testes or the skin. The yaws strain, however has a rather long incubation period with the development of lesions which are less extensive and much less indurated than those produced by the syphilis strain The bejel strain appears to lie somewhere between the other two groups, in terms of pathogenicity Although Leon y Blanco and Oteiza have reported on the successful inoculation of pinta treponemas into the scrotum of rabbits this observation has not been corroborated by others

Transmission experiments. In 1938, Leon y Blanco inoculated himself and other subjects with material containing T carateum and successfully produced the initial lesion on the skin, which appeared 7 to 10 days after the inoculation Recent studies of our group, carried out in Iguala, Mexico have shown that it was not possible to transmit pinta by blood transfusion. Such findings are in agreement with the fact that no case of accidental transmission of pinta by blood transfusion has been reported.

IMMUNOLOGY

Although it is generally agreed that pinta in its late stage confers immunity against reinfection and superinfection, there has been some controversy regarding cross-immunity between pinta and syphilis Leon y Blanco has shown that pinta can be success-

fully inoculated in patients with syphilis, and more recent reports indicate that pinta does not confer immunity to syphilis. In parts of Venezuela, where yaws is common, Briseno Rossi and Iriarte reported on the lack of cross-immunity between pinta and yaws They have observed the development of pinta lesions in twenty persons who had yaws and approximately the same number of pinta patients who subsequently developed yaws lesions. All these studies seem to indicate that the different strains of treponemas do not confer immunity against each other

SEROLOGY

According to previous surveys, the routine serologic tests for syphilis are negative in the primary stage of pinta, whereas they are positive in the secondary stage in 60 per cent of the patients. In the tertiary stage, positive reactions have been reported in from 70 to 100 per cent of cases. According to recent serologic data obtained in the examinations of sera from a group of 157 pinta patients of the State of Guerrero, we noted that the serologic tests for syphilis were frequently positive in the primary stage. Moreover a higher incidence of positivity was found in the secondary stage.

The results obtained in this survey clearly indicated that serologic tests began to give positive reactions from two to four months after the onset of the disease and independently of the stage of the disease. As soon as these tests became positive, they continued to show a progressive increase of serologic titer The highest titers were obtained in the intermediate type of late cases, where it was not uncommon to find 1024 dils or more. In the primary stage 81.8 per cent of our patients gave positive reactions, and 97.2 per cent positive reactions were obtained in our patients in the secondary stage. With the advance of the more purified antigens utilizing cardiolipin, it was hoped that it would be possible to differentiate pinta from syphilis. It was soon found that all of the treponemal infections, including pinta, produced positive reactions. In fact, a higher incidence of positivity was obtained with cardiolipin antigens than with the cruder lipoidal antigens, because of the increased sensitivity of the former

Various special laboratory procedures have been devised, with the hope of differentiating syphilis from the other treponemal infections Among these are the Khan "verification tests" Chargin and Rein subjected the sera of 268 patients with pinta to one of the Khan verification tests All gave strongly positive reactions with the routine serodiagnostic tests varying from 4 to 160 units with the Khan quantitative test. Of these, 225 (83.0 per cent) gave the syphilitic type of reaction, 17 (6.3 per cent) gave the general biologic (nonsyphilitic) type, and the remaining 26 (9 7 per cent) gave the inconclusive results.

The Euglobulin Inhibition Procedure devised by Neurath has been found to be of value in differentiating syphilis from nonsyphilitic diseases and conditions. It has not, however been of any help in differentiating pinta or yaws from syphilis in our series of sera examined in the serologic laboratory at New York University

More recently Nelson and his associates have developed a serologic procedure for the detection of a specific antibody in treponemal infections This specific test has proved to be of tremendous value in differentiating true from false positive reactions. Khan and his associates tested various strains of T pallidum, T pertenue and T canaliculi with "standard" pools of sera from animals infected with each of the strains. These studies indicated a significant immunogenic difference between the syphilis and yaws strains on the one hand and canaliculi strains on the other but not substantial difference between the syphilis and yaws strains tested. However the studies were limited to a few strains which had been separated from their natural hosts for 10 to 15 years. Similarly it has not been possible to differentiate the syphilis from the pinta strains by this specific procedure

During the Mexican Pinta Study it was noted that the Khan Standard, the Rein Bossak, and Marquez Rein-Hazay tests gave many zone reactions This unusual phenomenon has been observed by other investigators with most of the macro- and microflocculation tests. Although such zone reactions are occasionally observed with high titered syphilis sera and somewhat more frequently with sera from yaws patients in our experience it occurred more frequently with pinta sera.

SYMPTOMATOLOGY

Lesions of pinta are so varied and so intermingled in the course of the disease, that classification into sharply delineated stages, as is the case of other treponemal diseases, is almost impossible. The classification employed in our studies is as follows

Primary stage. The first manifestation of the disease is the initial lesion. In our experience with the naturally acquired infection, the development of the primary lesion is similar to that described in experimentally induced infections. We have observed that primary lesions of approximately 15 or 30 days appear as small lenticular slightly scaly papules, approximately one centimeter in diameter In about one to two months these lesions reach a diameter of two to three centimeters, and their appearance changes. *The lesions at this stage are usually of three types:* erythematous, circinate, or psoriasiform, with the last type occurring predominantly in older lesions. The erythematous, scaly lesions are slightly elevated plaques of oval or irregular shape. The circinate lesions are slightly scaly and erythematous, with an annular outline and slightly elevated borders. The psoriasiform plaque is a scaly reddish salmon or reddish white, sharply marginated lesion.

In all types, but chiefly in the last, the primary lesion may continue to increase slowly in size and reach sometimes a diameter of 10 centimeters or more in about one to two years. Frequently the older lesions are surrounded by smaller satellite lesions which may fuse with them and form a large configurate pattern. These older primary lesions develop varying shades of pigmentation which coexist frequently with hypochromic and achromic areas. When the primary lesion heals, there is usually a leukodermic area at the original site.

The distribution of the primary lesion, in order of frequency is as follows lower extremities face, neck, upper extremities, chest, buttocks, and abdomen. Lesions of the lower extremities appear on the legs, dorsum of the feet, ankles, and knees. Lesions of the face occur on the chin, cheeks, eyelids, and upper lip. Primary lesions of the genitalia and scalp have not been observed in our series of patients.

Secondary stage. Secondary lesions develop from one month

to one year or more after the appearance of the initial lesion. Sometimes they are scarce, only two or three occurring, but they may be numerous Extensive dissemination as in syphilis, is a rare occurrence. Primary or secondary lesions may have a similar appearance (circinate, psoriasiform, or erythematous-scaly plaques) Occasionally the lesions become secondarily infected and show impetiginization with crusting. In analogy to syphilis, Latapí and Leon y Blanco suggested the term "pintides" for these secondary disseminated lesions which appear on the same sites as the primary lesions. The genitalia, groins fossa axillaris, and scalp are usually not involved.

Initially pintides are erythematous with some scaling but later they become pigmented, first appearing copper colored, then lead-gray and after some time slate-blue. Although some lesions undergo pigmentation only after several months, others change color during the first month. It depends a great deal on the location of the lesions. Those on the covered parts of the body pigment very slowly or not at all, whereas lesions located on uncovered parts become pigmented quite rapidly From three months to one year most of the pintides show gradations of depigmentation, either centrally peripherally or irregularly in small areas. Often pintides have a mottled appearance caused by alternating patches of erythema, pigmentation, and leukoderma. Finally the regressing pintides may become completely depigmented Although this achromia occurs more frequently six months to one year after the appearance of the pintides, it may occur earlier It is not rare to see leukoderma develop in some patients within three months after the appearance of the secondary lesion (early leukoderma)

Pintides may recur either early (1 to 2 years) or late (10 years or more in the course of the disease) Recurrent pintides may appear on the same site as the original lesions but they are usually less numerous and frequently larger sometimes reaching a diameter of 10 centimeters or more Although they may be psoriasiform or circinate, they usually occur as erythematous scaly plaques with ill-defined borders. This type sometimes becomes keratotic, especially when located on the legs, knees, ankles, wrists elbows and loin. In some instances, new erythe-

matous, recurrent plaques intermingle with the pigmented and leukodermic areas resulting from the original pintides, so that diffuse, extensive, polychromic areas are formed, sometimes arranged on the extremities in sleevelike fashion. It is difficult to classify such patients since they have secondary and late pinta lesions at the same time (intermediate type) Recurrent pintides undergo the same regressive achromic changes as noted on the original disseminated lesions.

Tertiary (late) stage. Leukoderma represents the terminal phase of the disease. Classification, however of this stage, is also extremely difficult since it does not necessarily reflect the duration of the disease but rather the rate of regression to the achromic phase. This may occur as early as three months following the onset, yet we have observed many patients with this achromic phase. This may occur as early as three months follow pintides for many years. Therefore, some patients may present the late stage with achromic lesions in a few months, while other patients may continue to develop recurrent secondary lesions for many years. The late changes proceed in an irregular fashion allowing an intermingling of all varieties of dyschromia, hypochromia, and achromia. The dyschromic lesions appear chiefly on the face and with less frequency on the hands, wrists, forearms, legs, and feet. The hypochromic lesions appear on the thighs, legs, buttocks, forearms, arms, back, and chest, whereas the achromic areas appear over the bony prominences. In pinta of long duration, poikilodermalike atrophic changes may occur usually on the forearms and back of the hands and legs.

Leukoderma or "white pinta" represents the terminal stage of the disease, either as a result of adequate therapy of old cases or in those patients who, without treatment, become spontaneously cured" after many years.

HISTOPATHOLOGY

In contradistinction to other treponematoses, where clear-cut histopathologic differences between one stage and the other are found, such differences are minimal in pinta. The differences are more closely related to the age of the lesions than to the particular clinical stage.

Primary and secondary lesions show similar histopathologic pictures. At first, there are moderate acanthosis and slight spongiosis with a moderate inflammatory infiltrate in the upper portion of the dermis. The infiltrate, which is chiefly located around the dilated blood vessels, consists primarily of lymphocytes with some histiocytes, plasma cells and polymorphonuclear leukocytes. The pigmentary changes are minimal and as the lesions become older there is some evidence of mild hyperkeratosis and parakeratosis, especially in the psoriasiform type. Other lesions are characterized by the presence of lichen planuslike changes, which consist of hyperkeratosis, granulosis, and some liquefaction degeneration of the basal-cell layer Keratotic follicular plugging may also be present, as well as vacuolization of the prickle-cell layer The lichen planuslike changes are more frequent in cases of long duration or in recurrent secondary lesions.

Pigmentary changes are characteristic of the older primary and secondary lesions and consist of a decrease of melanin in the basal-cell layer with a deposit of the pigment in the dermis. Hasselmann also described the decrease or absence of pigment in the deeper strata of the rete Malpighii with a deposition of pigment in the dermis, either in clumps or around the blood vessels. In a few instances, however increase of pigment is found, both in the basal and the dendritic cells, with intermingled areas of decreased and increased melanin.

Late intermediate or dischromic lesions show changes similar to those described above. The leukodermic areas are characterized by the disappearance of the pigment in the epidermis and by few inflammatory changes. In cases of very long duration poikilodermalike atrophic lesions may be found, consisting of atrophy of the epidermis with thinning of the rete pegs, dilatation of the superficial vessels in the dermis, liquefaction degeneration of the basal-cell layer degeneration of the collagen, and destruction of the elastic fibers. Hair follicles and sebaceous glands are absent.

TREATMENT

Pinta, like other treponematoses, has been treated for many years with heavy metals with indifferent results.

In the first Mexican mass study of pinta, we treated a group of 665 pinta patients and demonstrated the possibility of a satisfactory clinical and serologic response by the use of a single dose of 1,200,000 units of procain-penicillin G in oil with 2 per cent aluminum monostearate (PAM) Since that time, this repository penicillin as well as the broad spectrum antibiotics have been employed in many thousand of cases. Although the broad spectrum antibiotics have been effective, the response is slower and the darkfield disappearance time of treponemas from the lesions is longer than with penicillin. Recently a new penicillin salt (N N dibenzylethylenediamine dipenicillin G) has been introduced for the treatment of syphilis. Due to its extremely low solubility in water penicillin blood levels can be prolonged over longer periods of time than with PAM.

My associates and I recently reported on the value of a new combination of three penicillin salts (Panbiotic Bristol Laboratories) in the treatment of treponemal diseases. A single dose of 2 ml. in aqueous suspension provides 800 000 units of potassium penicillin G 800 000 units of procaine penicillin G and 600,000 units of N N dibenzylethylenediamine dipenicillin G This combination was conceived by Buckwalter and Dickinson on the basis that the solubility variations of each penicillin salt when ad ministered as a single intramuscular injection should provide an initial high blood concentration within an hour an intermedi ate blood concentration for 24 to 36 hours, and a prolonged blood concentration for at least 15 days or longer in the majority of patients.

We have treated a series of 665 pinta patients with PAM and 68 patients with Panbiotic. All patients were subjected to serologic examinations immediately prior to therapy and at varying intervals following completion of treatment for periods up to two years. The majority of patients treated with PAM received 1.2 million units in a single injection, whereas all of the patients in the Panbiotic series received a single injection of 2.4 units. Of the 19 patients with primary lesions all (100 per cent) were cured. Of the 186 patients with secondary lesions, 138 (74.2 per cent) were cured, and the remaining 48 (25.8 per cent) were improved. Of the 213 patients with late pinta (many of whom were classi-

fied in the intermediate type) 97 (45.6 per cent) were cured, 98 (46 0 per cent) were improved, and 18 (8.4 per cent) showed no improvement at the time of their last examination. The pigmented and hypochromic lesions disappeared in two to four months whereas the early leukodermic areas repigmented in three to five months. The late leukodermic lesions of five years duration or longer required one year or more for partial repigmentation.

The serologic improvement was much slower in that approximately only 20 per cent attained serologic cure (seronegativity) 50 per cent showed serologic improvement, 20 per cent showed no serologic improvement (serologic fastness) and 10 per cent developed a serologic relapse (either treatment failure or reinfection)

From these studies we feel that a single injection of repository penicillin is highly effective in the treatment of pinta. The results obtained with Panbiotic (2.4 million units) appeared to be better than those obtained with PAM (1.2 million units)

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Viral Diseases of Interest to the Dermatologist

By

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THE VIRAL diseases of the skin offer an accessible and excellent field for experimentation and study in which even human inoculation is possible. Unfortunately especially trained personnel and well equipped laboratories are essential for investigative studies. In this brief presentation of our present knowledge on the subject, I shall limit myself mainly to a discussion of the natural history of dermatologic conditions caused by viruses, stressing the problems of pathogenesis and immunity and adding a few words about treatment. Only the highlights of this rapidly changing chapter of medicine are presented here.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a purely human disease; all attempts to inoculate animals have failed. It is most common in children but may be seen at all ages I once observed a patient 81 years of age in whom the infection could be traced to his grandson.

In typical cases the rounded, semiglobular waxy white or pink, semitranslucent, firm growths with a depressed center are easy to diagnose. However occasionally secondary infection of pyogenic origin occurs masking somewhat the characteristics of the disease. Sometimes the lesions are minute pointed papules only visible through a magnifying glass. The incubation period varies between two and six weeks.

Although the virus of molluscum contagiosum is one of the earliest known as the cause of disease in humans its study has been hampered because it can not be inoculated into animals or cultured in chick embryos.

As early as 1907 Lipschutz studied this disease and found minute, pink-staining bodies which he proved to be elementary bodies, the actual cause of the disease. Later these were called "Lipschutz bodies. Under the electron microscope the elementary bodies are rectangular with a tendency for pairs to join at corners and to cluster together giving a mosaic appearance.

Histopathology The lesion is closely packed with pea-shaped lobules, the epidermal cells undergoing a peculiar degeneration. Ebert and Otsuka have shown that the molluscum body is really an overgrown cytoplasmic inclusion due to the action of the virus, that it has shrunk away from remnants of the cytoplasm, and that it houses myriads of elementary bodies, doubtless the virus. Blank and Rake recommend referring to the readily extended center of the molluscum lesion as the core rather than the "molluscum body"

The virus of molluscum contagiosum together with those of the lymphogranuloma psittacosis group compose the largest group that infect human beings.

Pathogenesis, immunology and epidemiology The virus is strictly epidermotropic, affecting only the skin and rarely the mucous membranes (conjunctiva, genitals) The viscera are not known to participate in the infection. In many cases apparently no immunity is obtained, hence the danger of autoinoculation by the patient. The virus is constantly being extruded from the lesions to the surface of the skin but probably an abrasion or a solution of continuity on the skin is necessary for its development. The disease may be transmitted by direct contact among children through infected hands and towels as well as in beauty salons, gymnasiums, and turkish baths.

Blank and Rake mention that several attempts to induce experimental lesions in adults by inoculation of fresh concentrated viral suspensions produced no clinical lesions but an immune reaction of the tuberculin type with small, red papules in 48 to 72 hours, disappearing in five to seven days. They believe that this observation corroborates the theory of immunity without clinical disease being due to a previous inapparent infection.

Laboratory diagnosis. A thin spread of the contents of one lesion under darkfield illumination will show the elementary par

ticles If a drop of an isotonic solution is added, the brownian movement of the elementary bodies will be noticed. Wet preparations of Lugol's solution or stained preparations of Mann's method will show the inclusion bodies.

Treatment. The disease rarely disappears spontaneously and does not seem to respond to the power of suggestion. I have found simple curettage of the lesions followed by the application of silver nitrate stick most effective. Recently I had success with applications of podophyllin, 25 per cent in tincture of benzoin. Multiple punctures of the lesion with a clean needle or pressing out contents through the central opening is also usually effective. Systemic treatment with the sulfonamides, aureomycin, or chloromycetin has been advocated but in my experience has been discouraging

HERPES SIMPLEX

It is now generally accepted that the clinical appearance of the lesions caused by the virus of herpes simplex in humans depends on the affected tissue and the immunologic situation of the host.

The disease follows a definite pattern characterized by a primary infection and a latent stage during which the virus is subject to reactivation through the precipitating action of a trigger mechanism. Recent studies have shown that the primary infection in most individuals is asymptomatic; this probably occurs in early childhood. In about 1 per cent of the population, the first contact by the virus with virgin soil, usually a child, results in a violent reaction of the host tissue against the invading virus with systemic changes.

The mucous membranes seem highly susceptible, and the disease manifests itself in the form of acute herpetic gingivostomatitis or vulvovaginitis. Intact skin is more resistant, but when implanted on eczematous skin, the virus produces an extensive vesicular eruption. In the case of eczema, the clinical picture is referred to as Kaposi's varicelliform eruption, although the name eczema herpeticum (Lynch) is more appropriate as the same clinical picture can be produced by the virus of vaccinia.

Neutralizing antibodies appear in the blood following the primary infection.

After the virus has penetrated the body it may remain latent for years, in fact it may never be reactivated, but under the precipitating action of a trigger mechanism such as a febrile disease, exposure to cold, trauma, menstruation, or sometimes without apparent reason, the lesions reappear This time however the eruption is milder and is usually limited to the lips or the penis or any other part of the body This time no systemic changes occur The condition is notorious for its tendency to relapse on the same area. The observation that patients with circulating antibodies are subject to relapses when the antibodies in vitro rapidly neutralize the virus has been explained by the fact that the virus is an intracellular agent and possibly not reached by the antibodies.

The virus of herpes simplex measures 175 millimicrons in stained preparations and is somewhat smaller when studied through the electron microscope. The eosinophilic inclusions called Lipschutz bodies occupy almost the whole nucleus of the epidermal cell. In humans, the lesions appear on the skin, mucous membranes, the eyes, and the nervous system, indicating that the virus is ectodermatropic.

The assistance of the laboratory is seldom needed in the diagnosis of the average case. When unusual eruptions are under study different methods of investigation are possible. Blank and his associates, using a technique similar to the one used in the Tzanck test, have shown that the cytologic diagnosis of smears is helpful. Although the cytologic features encountered in herpes simplex, herpes zoster and varicella are the same, and the differentiation among these diseases, especially between herpes simplex and herpes zoster requires other tests, cytologic studies are helpful in ruling out all other vesiculobullous diseases

Practically all commonly used laboratory animals are susceptible to inoculation with the virus of herpes simplex. The most popular technique is inoculation of the rabbit's cornea by scarification, which causes keratoconjunctivitis in from 12 hours to one week. Intracraneal injection results in encephalitis which is invariably fatal. The chorioallantoic membrane of embryonated eggs is susceptible to the virus, and this method is rapidly supplanting animal inoculation.

Nagler has devised a skin test using an antigen prepared from

amniotic fluid of inoculated yolk sac. Intradermal injection of this antigen produced an inflammatory papule at the site of injection after 48 hours. This test parallels the presence of antibodies in the serum and is positive in most adults, showing that at sometime these persons have been invaded by the virus. Serologic tests help to demonstrate primary infections, since they show a rise in the antibody-titer during convalescence.

Microscopic examinations of tissue of either primary or recurrent herpes simplex shows intraepidermal vesicles with ballooning degeneration and is indistinguishable from herpes zoster and varicella. Intranuclear inclusions are abundant in multinucleated balloon cells.

Treatment. The antibiotics have been disappointing, except possibly aureomycin in eczema herpeticum. In one case, I felt that aureomycin was helpful. For relapsing cases, repeated vaccinations with smallpox vaccine is occasionally of value.

HERPES ZOSTER

Because of its typical bandlike appearance following the distribution of a nerve, herpes zoster was mentioned very early in medical literature as zona by the Greeks the name still being used by the French and Spanish.

As early as 1888, Von Bokay suggested the possibility of a relationship to varicella, mentioning in support of his concept that children who have been in contact with a patient with herpes zoster commonly develop varicella. Both diseases seem to produce a lasting immunity to their own viruses Wise and Sulzberger suggested that herpes zoster is possibly a relatively immune form of varicella which occurs in those whose tissues have been specifically changed in their capacity to react, through previous acquaintance with the same virus. This may have taken place in a clinical disease (varicella) or have been subclinical.

Stokes, Jr believes that varicella virus affects the general population at an early age and that in some instances the virus may remain in the nerve cells. In these individuals later in life, a precipitating factor such as exposure to cold, trauma, or pressure will precipitate a localized virus-activity along the posterior root fibers with subsequent development of herpes zoster Blank and

Rake believe that there is now sufficient evidence to consider chicken pox and herpes zoster different clinical manifestations of infection with the same virus. They are of the opinion that the relation of chicken pox to herpes zoster is analogous in many ways to that of the primary and recurrent manifestations of herpes simplex.

Etiology The zoster virus under the electron microscope is approximately 210 millimicrons in diameter brick shaped, and has a dimple in the center Rake has shown that the morphology of the viral particles is the same in chicken pox and herpes zoster Nagler and Rake have shown that it is sufficiently distinctive to differentiate these diseases from smallpox or vaccinia. Goodpasture and Anderson have succeeded in inoculating the virus on human skin grafted on the chorioallantoic membrane of the embryonated egg.

Two types of herpes zoster have been described the "primary" which appears without any apparent precipitating cause and the "secondary" which appears either in the course of febrile diseases or following trauma or the administration of arsenic, bismuth, etc., or in patients with malignancies and lymphoblastomas. The differentiation is not always easy and many cases thought to be "primary at first are later shown to be secondary to a hitherto unrecognized disease such as leukemia. In cases of primary infection, the virus presumably reaches the ganglia through the skin or through the blood stream after implantation on the pharynx. In secondary infections, the virus is possibly activated by the precipitating factor after a latency in the body In lymphoblastomatous disease, pressure or actual infiltration of the nerve roots may be the activator

The pain of herpes zoster is most irregular in severity and character It is usually said that the older the patient, the more severe the pain. It may precede, accompany or follow the eruption. Every clinician knows that postherpetic pains are most resistant to therapy After Combes and I published our article on the treatment of herpes zoster we received many letters from all over the country from patients with postherpetic pains. Some of these people had had the disease for several years and had received every conceivable method of therapy to no avail.

Treatment. Local treatment of mild cases is not necessary other than to cover the lesions with a simple lotion. Protection from exposure to air and friction seems beneficial. When I was an assistant to the late Dr Howard Fox, we often found the spraying of the lesions with paraffin quite effective.

Internal treatment varies from the use of acetylsalicylic acid to that of cortisone. Autohemotherapy thiamine hydrochloride, posterior pituitary extract, cobra venom, vasodilators, and other methods have been found to be effective by different investigators. My experience with ACTH and cortisone has been disappointing

Combes and I have made a study of dehydroergotamine-45 (Sandoz, DHE-45) and protamide. The former is a derivative of ergot and is often used in the treatment of migraine Protamide is a denatured proteolytic enzyme obtained from the mucosal layer of the hog stomach. Both medications are given intramuscularly In both, the results were satisfactory in about 75 per cent of cases. The best results were obtained in cases of "primary" herpes zoster In cases of postherpetic pains, there was little or no improvement. It was noticed that none of the patients who received protamide later developed postherpetic pains.

VERRUCAE

Most investigators believe that a single etiologic agent is responsible for all forms of verruca. There is experimental evidence in favor of this concept, since inoculations of filtrates of different types of warts have produced only verruca vulgaris in susceptible individuals.

It appears that the clinical picture of a lesion caused by the verruca virus depends on different factors, one of them being its location on the body The back of the hands fingers, and forearms are most commonly affected by verruca vulgaris and verruca plana, while the thinner skin of the eyelids as well as the sides of the neck and axillae are more often affected by verruca digitata and filiformis the moist genital and perianal areas are more prone to develop condyloma acuminata. The thickened skin of the soles usually at the sites of pressure develop verruca plantaris.

The influence of pregnancy is an interesting factor It is known that verruca filiform and condyloma acuminata are prone to de-

velop during pregnancy and often disappear spontaneously after parturition. In these cases, it seems that infection or contamination is not important, possibly because the virus is already present on the skin, and pregnancy acts as a "trigger mechanism" for the appearance of the lesions, a mechanism similar to that occurring in herpes simplex.

Immunology Every dermatologist has had opportunity to see individuals with lowered resistance to the virus of verruca. These patients usually present two or three types of verruca, and their treatment is often unsuccessful. It is possible that some individuals are immune to infection with the verruca virus. The fact that verruca is uncommon after the age of 40 may indicate that some degree of immunity has been developed. It is not uncommon to see brothers or sisters of patients with verruca vulgaris entirely free of lesions in spite of the fact that they are in constant intimate contact with the patient. Findlay after three successful inoculations on himself, became immune to further inoculations.

Etiology There is no general agreement among investigators as to which structures represents the virus in tissue. Strauss, Bunting, and Melnick described eosinophilic bodies in large vacuolated nuclei of epidermal cells. Blank, Buerk, and Weidman regard these structures as nonspecific, because they fail to give the histochemical reaction characteristic of viruses.

With the use of the Feulgen stain to demonstrate the presence of desoxyribonucleic acid (DNA) in inclusion material, Blank and his associates detected round basophilic intranuclear inclusions in the prickle and granular layers of warts. These inclusions are surrounded by a clear zone of ballooning degeneration producing "bird's-eye" cells. It is interesting to note that these changes were found by them only in half of their cases and by Strauss and his associates in an even smaller percentage. Characteristic changes in the latter series were observed only in lesions less than nine months old.

Logically the correlation between the clinical types of wart and the presence of inclusion bodies would yield interesting information. Based on their clinical and laboratory study of 102 warts, Lyell and Miles divided their material into two groups: one which they considered a separate clinical entity in which inclusion bodies

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Although this is a systemic disease, the main pathologic changes occur in the region of lymphatic drainage of the primary lesion. This is usually on the genitals or in the rectum, thus causing the two main clinical pictures of the disease the primary lesion-inguinal adenitis type and the anorectal-genital syndrome. Systemic changes such as fever malaise, headache, arthralgia, and toxic eruptions are common. The erythrocyte sedimentation rate is increased and there is a hyperglobuleania with reversal of the A/G ratio

The laboratory diagnosis generally is made by the Frei test. The complement fixation test is also helpful. Positive tests are not diagnostic in the absence of a clinical picture, since they only indicate that the patient is or has been affected by the lymphogranuloma venereum virus.

The virus of lymphogranuloma venereum belongs to the group of large viruses. They are often classified as Chlamydozoaceae which are related to the rickettsiae. Gay Prieto in 1927 described small bodies within monocytes in material obtained from a bubo of lymphogranuloma venereum. The virus can be cultivated in tissue culture and chick embryo.

The complement fixation test shows that there is similarity between this virus and the viruses of psittacosis and cat scratch disease. Meyer has stressed that the sera of patients with acute lymphogranuloma infections occasionally yields significantly high complement fixation titers in the presence of the psittacosis virus, but these fade during convalescence. This is in contrast with psittacosis infection in which the titer rises during convalescence and persists for many months.

Immunology Little is known about the immunologic situation of patients with lymphogranuloma venereum. Inoculation of a patient with material from his own bubo always produces an insignificant inflammatory reaction but no adenopathy It is possible that patients develop a lasting immunity I do not recall having seen a patient with a proved reinfection.

It should not be forgotten that lymphogranuloma venereum is a common cause of biologic false positive tests for syphilis

Treatment. It is important to remember that the response of the disease varies greatly in the different clinical types. The in-

guinal adenitis-type responds readily to most treatments and may subside spontaneously The anorectal-genital syndrome is more resistant, and even the best management may fail to eradicate the disease. In my experience, the biologic treatment with repeated intradermal or intravenous injections of Frei antigen have invariably failed. The intravenous injections of Frei antigen and the intravenous injections of typhoid vaccine have produced similar results in my experience· both acted probably by eliciting a nonspecific febrile reaction.

Excellent results are obtained in the inguinal adenitis-type with any of the sulfonamide preparations, and I still consider them the drugs of choice. The broad spectrum antibiotics are effective but more expensive and many mask a concomitant syphilitic infection. In the anorectal syndrome these medications should be used in long courses, possibly alternating and combining them. Other methods of therapy such as rectal *dilatations* and surgery may be required, since chemotherapy may be ineffective.

VIRAL (DERMATOLOGIC) DISEASES CONTRACTED FROM ANIMALS

The following four diseases of viral etiology have in common the fact that they are usually contracted from animals.

1 Milkers nodules. This disorder is due to a virus which is different from that of vaccinia attempts to demonstrate inclusion bodies have failed. The disease is apparently caused by contact with "natural" cowpox on the teats or udders of cows. The incubation period is approximately one week. The lesions are reddish-blue firm, raised, single or multiple nodules. They may resemble pyogenic granuloma. Occasionally there are lymphangitis and regional lymphadenitis. Histologically the lesions resemble verruca vulgaris, although these are more infiltrates and less epidermal changes. No treatment is necessary unless secondary infection is present.

2. Ecthyma contagiosum (Orf) In sheep orf is manifested by pustular and ulcerative lesions of the skin and mucous membranes. The condition may be contracted by persons in contact with either living or dead, infected animals The saliva seems to

be especially contagious, since even dry saliva crust has been found infectious for several months.

After a short incubation period of possibly a few days, a lesion appears on the hands and occasionally the face. At its onset, the lesion is a dusky red, firm, painless papule. It grows rapidly and may reach several centimeters in diameter Its summit is ulcerated, the depressed center being covered with a white membrane which may exude a serous material when broken. It may resemble a large molluscum contagiosum or a primary vaccination "take." Secondary infection may produce lymphangitis and lymphadenitis

The virus has been cultivated on chick embryos humans and animals have been experimentally inoculated. The disease is usually occupational, as in Hodgson-Jones series of eight cases of whom six were porters in a meat market, one a butcher and one a housewife. All had handled sheep heads and often scratched their skin with the teeth of the dead animals. Agglutinins were detected in the serum of Goldsmith's patient as late as 182 days after infection. The disease is self limited, lasting approximately five to eight weeks. No treatment is usually necessary unless secondary infection develops.

3. Foot and Mouth Disease. This is an extremely infectious disease which affects primarily cattle but also goats, sheep, and pigs. The virus is of low infectivity to man and is acquired by ingestion of contaminated food or by handling affected animals. At present the disease is the subject of an intensive campaign, especially in Mexico, where it is endemic. The most effective method of control is the ruthless slaughter of the susceptible host.

In man, after an incubation period of two to ten days, the patient develops systemic symptoms with burning of the mouth followed by vesicles which break to form erosions and ulcerations. Similar lesions appear on the palms, soles, and in the interdigital spaces. There is no specific treatment.

4 *Cat-scratch disease (Benign inoculation lymphoreticulosis)* This self limited disease is usually benign and involves a group of lymph nodes depending on the site of inoculation. Frequently but not necessarily the disease is acquired by the scratch of a cat Within a few days, the scratch site becomes inflamed,

and a papule or ulceration appears, after which adenopathy usually develops within two to four weeks. As the site of inoculation is usually the hands the axillary nodes most often become involved. The nodes are usually tender and the overlying skin is inflammed. They may be freely movable or fixed by the perinodal infection. The nodules may suppurate and form a discharging fistula. When adenopathy is fully developed, there are some systemic symptoms, and an erythematous maculopapular eruption may occur

An intradermal test prepared in the same manner as that of the human Frei test is specific. Sections of the node prepared with special stains reveal the presence of intranuclear and intracytoplasmic inclusion bodies. The virus is assumed to belong to the psittacosis-lymphogranuloma venereum group. Complement fixation tests with chick embryo Frei antigen have been found positive in a variable number of cases.

In the differential diagnosis, tularemia, tuberculous adenitis, pyogenic infections, and lymphogranuloma venereum should be considered. The Frei test is usually negative, a finding helpful in the differentiation from the latter disease. The fact that veterinarians have not seen this condition in cats would indicate that these animals are only carriers of the disease. It has been suggested that the virus is probably widely distributed in vegetable life.

The disease responds to treatment with aureomycin or chloromycetin.

DISEASES OF POSSIBLE VIRAL ETIOLOGY

In recent years, many other diseases of the skin have been attributed to a virus. I shall limit myself to a discussion of pityriasis rosea and leukemia.

There are some important factors in favor of a viral etiology of pityriasis rosea. *Brocq is credited with having produced one or* several primary lesions by inoculations in several areas. These were followed after a second incubation period by a generalized eruption. The seasonal incidence in spring and fall and the apparent immunity which develops are also arguments in favor of the infectious nature of the eruption It is also known that mild constitutional disturbances may accompany widespread eruptions.

The etiology of leukemia has long been a source of concern to all investigators. Gross has recently presented a working hypothesis of the "vertical" transmission of the leukemias which, in my opinion, deserves careful consideration. He believes on the basis of his experiments on mouse leukemia that there may be a group of submicroscopic oncogenic agents individually distinct, some causing leukemia and others, malignant neoplasia, which are transmitted directly usually through the genic cells from one generation to another These agents may exist in an inactive form, frugal and moderate in their requirements and causing no apparent harm to their carrier host.

Occasionally however prompted by as yet obscure but presumably varied trigger stimuli, these masked agents may change into formidable pathogens, causing rapid multiplication of the cells harboring them and resulting in leukemia or other malignant neoplasia. Since the oncogenic agents do not become activated in many instances, leukemia or other malignant neoplasia develops only occasionally in those members of families that carry and transmit the oncogenic agents.

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26

The Eruptive Fevers

By

Edward S. Petersen and Harlan M. Levin

THIS CHAPTER deals with the commonplace eruptive fevers, both bacterial and viral, most frequently encountered in large areas of the Americas. The other diseases that may be considered to belong to this group, such as syphilis, the rickettsial fevers, dengue fever psittacosis, and cat-scratch disease are presented elsewhere (see pertinent chapters)

No attempt is made to give a comprehensive clinical description of each disease except where it is relatively new and not well documented. The dermatologic aspects as well as the immunologic and allergic phenomena of each disease are emphasized.

Scarlet fever There is at last essential agreement that scarlet fever is not a disease entity but is a manifestation of the erythrogenic exotoxin produced usually by several strains of beta hemolytic streptococci and occasionally by hemolytic staphylococcus aureus. The locus of the infection producing this exotoxin may vary though usually it is on the pharynx or tonsil. Horsters and Lodderstedt, however still consider the role of the streptococcus to be secondary to that of a virus. In some 90 per cent of cases, the erythrogenic toxin-producing streptococcus belongs to Group A, identified by means of a group-specific carbohydrate called "C Substance" in turn, the Group A streptococci are divided into some 49 strains by type-specific proteins called "M Substances."

Concerning the clinical picture, there is now considered to be no difference whatever as regards infectivity course, and complications between streptococcal rash, i.e., scarlet fever and streptococcal disease without it, except that in the latter instance the patient has either already developed antibodies against the

erythrogenic exotoxin, or the infecting organism does not happen to be producing any. The appearance of the rash and of the pharyngitis with exudate, in combination with an elevated temperature, prominent, tender cervical lymph nodes, and a white blood count of at least 12,000 usually provides the bedside diagnosis.

When the diagnosis is in doubt, the injection of convalescent serum into the rash, with resultant fading, is helpful. This fading is known as the Schultz-Charlton reaction. It is negative in infectious mononucleosis, a disorder simulating scarlet fever in every other respect. Horsters and Lodderstedt claim that the "Doehle Body" a blue-staining, comma-shaped body is helpful in establishing the immediate diagnosis if more than one-third of the polymorphonuclear leukocytes contain it.

Successful culture of the beta hemolytic streptococci fails quite frequently; selective inhibition of the alpha streptococci which tend to overgrow the beta streptococci and the use of anaerobic cultures may be helpful. Contrariwise, a falsely positive throat culture may often be obtained because the beta hemolytic streptococci are frequently found in the carrier state. In such cases they do not usually develop a profuse growth on cultivation. However a definite diagnosis can not be made until a determination of the antistreptolysin or antistreptococcal hyaluronidase titers is made; these are found to increase in almost all cases of true beta hemolytic streptococcal disease and to remain unchanged in carrier states.

In their epidemiologic studies of beta hemolytic streptococcal infections, Dingle and his associates found no natural host other than man. The mode of spread may be direct or through inhalation of droplet nuclei or dust. A carrier state results when, during convalescence, the organism loses its specific protein, the M substance. This may be restored by animal passage. Rheumatic fever as a complication of scarlet fever follows Group A streptococcal infection of any strain with a uniform incidence of around 3 per cent. Glomerulonephritis, however follows infection with type 12, leading to a great variation in incidence depending on the strain involved in a given outbreak.

Penicillin is the drug of choice when therapy is continued for

at least seven to ten days, there is a definite decrease in the incidence of the early septicemic, and of the late complications, rheumatic fever and glomerulonephritis.

Meningococcemia. Recent interest in this disease has centered on epidemiologic and therapeutic studies. Type I meningococcus usually predominates during epidemics and types II and IIA during endemics According to Hedrick, the nasopharyngeal carrier rate during epidemics in confined populations may reach a level of 50 per cent. The death rate, despite the availability of effective therapy remains surprisingly high, around 0.6 per 100 000 population, which is about one tenth of the incidence of the pretreatment era. This may be due in part to great variations in the clinical picture, from a chronic recurrent septicemia to fulminating death within a few hours. The disease is currently the most frequent cause of sudden death in infants

The diagnosis is made on the appearance of the petechial or hemorrhagic rash and on cultivation of the organism. Sulfonamides remain the therapeutic agents of choice. The use of intravenous hydrocortisone in combination with ACTH has made possible the survival of a small number of fulminating cases with adrenal involvement.

Leptospirosis. This is a variety of infectious hepatitis caused by the organism Leptospira icterohaemorrhagiae. The term should also include diseases of a similar type caused by Leptospira canicola and Leptospira pomona. The course of leptospirosis may be divided into three stages the first or septicemic stage lasts for about a week and sets in with chills, fever and marked prostration, the second stage is marked by the occurrence of hepatic and renal damage as shown by icterus and the presence of albumin, casts, and red blood cells in the urine associated with cutaneous manifestations and the third stage, in which the leptospira gradually disappear from the blood and appear in the urine.

Cutaneous manifestations are present in only about 10 per cent of cases they are usually scarlatiniform morbilliform, or urticarial in type and are limited to the trunk.

The immunologic situation is characterized by the appearance of specific agglutinins and lysins in the blood during the second stage. A titer of 1:400 is diagnostic. In the third stage, lysis of

the temperature, drop in the icterus index, increase of the urinary output with disappearance of abnormal urinary signs, and reduction of hemorrhagic manifestations take place. In the third stage and thereafter the patient's serum will agglutinate virulent strains of leptospira in dilutions of 1:10,000 to 1 1,000 000.

The differential diagnosis includes idiopathic infectious hepatitis, acute yellow atrophy of the liver yellow fever infectious mononucleosis, rat bite fever and other eruptive fevers.

The most effective treatment is the use of hyperimmune serum obtained from horses whose blood has been hyperimmunized to an agglutinating titer of at least 1 100 000 The antibiotics have been relatively ineffectual.

Variola. The diagnosis of the isolated early case of smallpox is very important in preventing an epidemic; it can easily be missed because of the relative infrequency of the disease. Irons and his associates reported an outbreak occurring in the lower Rio Grande valley in which eight cases developed. There was one fatality The diagnosis of these cases was confirmed by cultivation of the virus on the chorioallantoic membrane of the embryonated egg Examination with the electron microscope of blood free vesicle fluid suspended in distilled water showed the differences between smallpox and chicken pox, the virus of smallpox being larger and more rectangular than that of chicken pox. Laboratory procedures now being used in diagnosis include the microscopic examination for elementary bodies, complement fixation tests, and neutralization techniques which employ pock counting on the chorioallantoic membrane of chick embryos.

The character of the rash is influenced by the resistance of the individual and the virulence of the virus. Previous vaccination reduces the severity of the eruption and the secondary toxemia. Scarring is also reduced. In resistant persons, the lesions are more superficially situated, and the progress from stage to stage is more rapid. In fact, some of the lesions progress from papule to crust so rapidly that lesions are present in different phases of development and develop in crops, thus creating a resemblance to chicken pox.

Treatment is symptomatic. In view of the severity of the disease and its relative ease of prevention, it is well worth while maintaining the effort to make vaccination universal The only

exceptions should be children with eczema, particularly in an active phase, since they are liable to develop generalized vaccinia, a condition distinct from Kaposi's varicelliform eruption.

Varicella. The surface complications of this disease are manifold and of serious significance. In order of frequency they are cutaneous abscess, lymphadenitis, erysipelas, gangrene, impetigo, paronychia, conjunctivitis, balanitis, hordeolum, blepharitis, stomatitis, and parotitis. Additional cutaneous complications are acute thrombocytopenic purpura and bullous and hemorrhagic lesions. The skin complications are caused by the exotoxins of streptococcal and staphylococcal infections superimposed on the lesions of varicella, particularly dermatitis gangrenosa, and cancrum oris and noma in children.

Three cases of severe primary varicella pneumonia have been reported in young adults. They were characterized by nodular pulmonary infiltrate, paucity of physical findings in contrast with the x-ray findings, clearing of the lung fields concomitantly with the disappearance of the rash, a negative blood culture, and the absence of leukocytosis. The occasional coexistence of herpes zoster ophthalmicus and chicken pox has long been known.

The typical microscopic changes found in cytologic smears of material obtained from patients with herpes simplex, herpes zoster and varicella are not sufficiently distinct to distinguish them individually There are large giant epithelial cells with one to eight nuclei present in the vesicles, the nuclei apparently being formed by amitotic division. The nuclei contain purplish Feulgen-positive material with blue-staining granules and green pigment. These findings serve to distinguish varicella from other vesiculobullous diseases.

Treatment is essentially symptomatic. In postvaricella encephalitis, however the steroids have been used with striking improvement. The danger of using steroids is nevertheless always present, as was shown in a patient in whom reactivation of the varicella virus took place after cortisone therapy Another patient developed varicella two years after an episode of giant urticaria brought on by penicillin therapy Ten days after the onset of varicella, he again developed giant urticaria following the application of penicillin ointment. He was then treated with cortisone, whereupon a typical chicken pox rash appeared.

should be taken only from those who are known to be convalescent rubella patients.

Erythema infectiosum. This disease which occurs predominantly in children six years of age or younger begins with red cheeks, varying from a diffuse erythema to closely grouped tiny papules on an erythematous base, flaring out from the nose, most intense beneath the eyes and fading toward the ears. After one or two days, an eruption appears on the arms thighs, forearms, buttocks, legs, trunk, and shoulders which varies from a diffuse mottled erythema to an eruption resembling erythema multiforme. Scarlatiniform, morbilliform, spotted purpuric, urticarial, and in one instance bullous lesions have been observed. After several days, the redness fades, often leaving an erythematous lacework with a *faintly cyanotic hue* especially on the *thighs*. Systemic manifestations are absent or mild.

Insect bites have been observed in about 20 per cent of the cases, and a resemblance to "chicken mite" dermatitis has been noted. As a possible vector the starling is implicated, and it is possible that a mite-transmitted virus is of etiologic significance. Of greatest importance are the diseases which must be differentiated scarlet fever measles, purpura, urticaria, lupus erythematosus and erythema multiforme.

Antibiotic and sulfonamide drugs are ineffective.

Exanthem subitum This disease is said to be the most common disease of childhood, 95 per cent of cases occurring between the ages of six months and three years. The incubation period varies between 10 and 15 days. There is then an abrupt fever of 39 C. or 40 C. which lasts for three to six days As the fever subsides, the rash makes its appearance in the form of pinkish, discrete *macules which fade on pressure* The individual lesions measure from 2 to 3 mm across and appear first on the trunk A palatal enanthem of red specks is often noted. Lymphadenopathy is present but not marked

The diagnosis can not be made until the rash appears, it being especially difficult because there may be an initial leukocytosis of around 15 000 after which leukopenia with relative lymphocytosis sets in by the third day The epidemiology is not well understood, cases tending to occur spontaneously somewhat in the manner

exceptions should be children with eczema, particularly in an active phase, since they are liable to develop generalized vaccinia, a condition distinct from Kaposi's varicelliform eruption.

Varicella. The surface complications of this disease are manifold and of serious significance. In order of frequency they are cutaneous abscess, lymphadenitis, erysipelas, gangrene, impetigo, paronychia, conjunctivitis, balanitis, hordeolum, blepharitis, stomatitis, and parotitis. Additional cutaneous complications are acute thrombocytopenic purpura and bullous and hemorrhagic lesions. The skin complications are caused by the exotoxins of streptococcal and staphylococcal infections superimposed on the lesions of varicella, particularly dermatitis gangrenosa, and can crum oris and noma in children.

Three cases of severe primary varicella pneumonia have been reported in young adults They were characterized by nodular pulmonary infiltrate, paucity of physical findings in contrast with the x-ray findings, clearing of the lung fields concomitantly with the disappearance of the rash, a negative blood culture, and the absence of leukocytosis. The occasional coexistence of herpes zoster ophthalmicus and chicken pox has long been known.

The typical microscopic changes found in cytologic smears of material obtained from patients with herpes simplex, herpes zoster and varicella are not sufficiently distinct to distinguish them individually There are large giant epithelial cells with one to eight nuclei present in the vesicles, the nuclei apparently being formed by amitotic division. The nuclei contain purplish Feulgen-positive material with blue-staining granules and green pigment. These findings serve to distinguish varicella from other vesiculobullous diseases.

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Rubeola. One of the most serious complications of measles is encephalitis which is most likely to occur during epidemics. Its incidence is 1 1000 cases in hospital admissions. This complication can be classified with the postinfectious type of encephalitis which appears unexpectedly when the rash has subsided, on about the third posteruptive day The mortality rate is from 10 to 30 per cent. The pathologic changes at first involve the blood vessels, with lymphocytic infiltration of the vessel walls. These changes are soon followed by perivascular demyelinization. The two theories concerning the pathogenesis of this complication are that it represents an inflammatory reaction and that it is a localized allergic response to the virus.

Considerable social and individual readjustments may be required following a complicating encephalitis Abnormalities of mental function can be demonstrated in a high proportion of cases after E.E G and neurologic evidences of disease have disappeared.

Great advances have been made with the electron microscope in identifying the virus of measles The virus is from 90 to 100 millimicrons in diameter grossly resembling that of influenza. It has no effect on those who have been prophylactically injected with immune serum globulin. It lives and multiplies for at least a week in the fertile hen s egg, where it is most easily grown. It passes the Seitz E K. disc under negative pressure and remains active after exposure to CO_2 ice at a temperature of −35 C. for four weeks. It is relatively sensitive to ultraviolet radiation which should provide a means of reducing air transmitted infections in schools.

Most effective in the treatment has been the modification with immune serum globulin. This is particularly desirable in children with siblings. 0 02 cc. of immune serum globulin per pound of body weight is used as soon as exposure has been determined, this amount being increased in very young or sickly children. It should not be given to children with an indefinite history of exposure, since the risk of developing homologous serum hepatitis is considerable.

Of 10 recipients of the same batch of plasma for measles prophylaxis, seven developed severe jaundice and three died.

One of the patients who died had symptoms of encephalitis without jaundice. Gamma globulin was then prepared by fractionation of this plasma. In 56 of the 55 recipients of this batch of gamma globulin, only one mild case of jaundice occurred, this being in a boy who had received 8.0 cc. This is a clear-cut instance of homologous serum hepatitis resulting from the administration of gamma globulin derived from plasma known to be icterogenic. Owing to the long incubation period, cases of homologous serum hepatitis may be overlooked, and it is therefore important to get a history of all previous injections in every patient with jaundice.

According to Watson, the use of the sulfonamides is of value to some children in preventing bacterial complications of measles.

Rubella. The rash in German measles varies from a barely perceptible macular eruption which may disappear in 24 hours to a diffuse erythematous scarlatiniform rash and flush which may take three to four days to disappear and which may leave a fine *desquamation without pigmentation.*

It has been shown that when the disease is contracted during the first trimester of pregnancy fetal development may be profoundly affected. A series of 78 cases of congenital cataracts of dense nuclear type in infants was reported from Australia, the mothers of these babies, with few exceptions, giving a history of having had rubella during the early part of their pregnancies. Forty four of this same group also had congenital heart disease, 15 of these infants dying within four years. The rubella syndrome of congenital defects consists of cataract, congenital heart disease, deafness, mental retardation, and microcephaly.

The causative agent is present in nasopharyngeal washings and in blood from patients obtained during the first day of the rash. Inoculation of this material into the nasopharynx of susceptible individuals produces typical rubella after an incubation period of nine to 16 days. Experimental rubella is contagious.

Present opinion is that in spite of the large increase in reported *cases of congenital abnormalities,* it is not desirable that the *mothers be subjected to therapeutic abortion,* particularly in view of the amount of protection given the fetus through administration of a known potent dose of immune serum globulin. Serum

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of infectious mononucleosis. The highest incidence occurs in spring and fall. A viral etiology is hypothesized.

No therapy is available.

The Coxsackie viruses and skin diseases. The Coxsackie virus group has recently been found to be the cause of a number of seemingly unrelated diseases, among them herpangina, pleurodynia, and aseptic meningitis. Because herpangina is associated with fever and pharyngeal and palatal lesions it may be confused with streptococcal pharyngitis or infectious mononucleosis. Furthermore, the causative agent of the 1951 Massachusetts epidemic exanthem might well be included in the Coxsackie group.

These are small viruses around 15 to 25 microgamma in diameter: they can be identified by injection into infant mice and through the development of neutralizing antibodies.

Herpangina has an incubation period of two to nine days after which a high fever sets in suddenly. Gray papulovesicular lesions surrounded by erythema appear on the tonsillar pillars, uvula, palate, and tongue. These number from two to 14, becoming yellowish and forming shallow ulcers up to 5 mm. in diameter. The fever usually does not last more than two days and the lesions not more than four. Coxsackie virus Type A has been isolated from the throat in 50 per cent of cases and from the stool in 80 per cent, an elevation of type specific antibody appears in 70 per cent. Children between six months and eight years are those most frequently affected, the highest incidence is from July to September. It is quite difficult to distinguish herpangina from herpetic gingivostomatitis, although the latter has a less abrupt onset and more lesions on the gums.

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Neva, Feemster and Gorbach have recently described a new epidemic exanthem. Their report includes cases from which Coxsackie virus and a new cytopathogenic agent were isolated. The rash appeared about a day after the fever subsided and consisted of pink or salmon colored, discrete, slightly raised maculopapules: the most common site was the face and upper chest. Oral lesions similar to those of herpangina were present in a few patients.

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Coxsackie virus was isolated from the stool and throat washings of a few patients but no increase in antibody titer developed. A different cytopathogenic agent, doubtless a virus was isolated from the stool of seven patients and grown on human kidney tissue culture- an increased antibody titer developed against this agent in all instances. This is probably the responsible organism, *a virus similar to but different in some respects from the Coxsackie* group.

Infectious mononucleosis. It is impossible to present a complete picture or satisfactory classification of this disease, since it can paint almost any picture whose colors include fever adenopathy pharyngitis headache rash, jaundice, abnormal leukocytes, and splenomegaly Variants and complications of many kinds have been reported, of which massive splenomegaly occasionally leads to splenic rupture, the only reported death from infectious mononucleosis being due to this complication.

The etiology remains undetermined, although recent studies point toward a viral origin. The studies of Wising conclusively demonstrate that Listerella monocytogenes, which was at one time thought to be the cause is in no way associated with the disease Wising was able to produce a similar illness after injecting infected lymph nodes into monkeys and once in five attempts in human volunteers He also carried out extensive pathologic studies of biopsied nodes and found intracytoplasmic cellular changes similar to those found in viral diseases

The highest incidence of the disease is around 20 years of age In college infirmaries, it accounts for some 2 per cent of admissions.

Sore throat, retroorbital headache, and fever are the most common presenting complaints and generalized lymphadenopathy and splenomegaly the most common findings The incubation period is believed to range from four to 20 days and possibly up to six weeks The onset is usually gradual, often with few physical findings but with such marked asthenia and irritability that a psychotic disturbance may be considered.

Recent surveys show that a rash occurs in from 5 to 10 per cent of cases Various eruptions have been described, such as maculopapular *urticarial morbilliform* erythematous, nodular and ery

thema multiformelike rashes. Even though a drop in platelets is not usually found, petechial and hemorrhagic lesions have been noted. A palatal enanthem consisting of about 15 pinhead-sized red spots has also been noted, the spots darkening in two days and disappearing in four Kallos reported a case in which the disease started as a painful ulcer of the penis.

The most common complication is hepatitis, jaundice and hepato megaly being found in up to 20 per cent of cases

The diagnosis always requires laboratory confirmation. Abnormal mononuclear cells always appear in the peripheral blood at some time during the course of the disease, and a rise in the heterophile antibody titer also occurs, as demonstrated by the Paul Bunnell test. Initially there may be leukopenia or increase in the polymorphonuclear leukocytes, but eventually the abnormal mononuclear cells which have a basophilic, foamy cytoplasm and an eccentrically placed nucleus appear in greatly increased numbers. They may constitute almost 100 per cent of a total leukocyte count of 80 000 The use of supravital staining has greatly facilitated the identification of the many different forms of mononuclear cells.

The status of the heterophile test, which consists of the agglutination of sheep red blood cells by heterophile antibody in the serum, has recently been much clarified by the work of Davidsohn. He considers it to be diagnostic if the titer is 1/224 or higher- if lower and there is any doubt as to the diagnosis, his differential test should be done. A portion of the serum is absorbed with guinea pig kidney If at least 1/8 of the titer remains, the diag nosis is confirmed, since heterophile antibody due to other causes such as horse serum injections is always completely removed. Next, another portion of the serum is absorbed with beef red blood cells heterophile antibody due to infectious mononucleosis is completely removed, other heterophile antibody persists.

There is no specific therapy Bedrest for the duration of the fever is important to prevent recurrences and hepatitis

Upon surveying the eruptive fevers as a group it is noteworthy that therapy is available for each of mortal consequences, save smallpox. Yet, from the diagnostic point of view nothing has been added to assist the physician at the bedside. True, current viral studies have elucidated the etiology of several of these disease-

and may be expected to clarify more. But these diagnoses are usually established by complex laboratory procedures several weeks after the recovery of the patient. From a practical standpoint, therapeutic activity can rarely be delayed even for the relatively quick growth of a bacterial culture. Study to bring new and immediate diagnostic aid for the early identification of the eruptive fevers would save many a ton of useless medication and obviate many a drug reaction.

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27

Rhinoscleroma

(RHINOPHARYNGEAL-LARYNGEAL SCLEROMA)

By

Esteban Reyes

RHINOPHARYNGEAL LARYNGEAL scleroma, a more appropriate designation which Nubleau and I prefer to rhinoscleroma, is a chronic, granulomatous disease of the respiratory tract, occurring from the nose to the bronchi with frequent involvement of the upper lip.

The disease is characterized by slowly developing sclerosis of the tissues of the respiratory tract, frequently resulting in extensive mutilation and unsightly disfigurement. It is neither hereditary nor contagious. The etiologic agent has not been definitely established.

In the Americas, the disorder is endemic in El Salvador and Guatemala and sporadic in the United States, West Indies, and South America, where it appears almost exclusively in foreign born persons. Women are more frequently affected than men. The disorder usually has its onset between the fifteenth and twenty fifth years of life, being rarely met with before the fifteenth or after the fiftieth year of life. It occurs in persons with a background of uncleanliness.

The disease is characterized by three stages of development.

The onset is insidious with symptoms of coryza, headache of the frontal-ethmoidal type, and a scanty malodorous nasal secretion. The patient usually complains of a dry throat. On examination, the nasal and pharyngeal mucous membranes appear injected and swollen.

The second stage is marked by the gradual disappearance of coryza. On the septum and the turbinate bones one sees small, hard, submucosal nodules. Occasionally one also sees them on the floor of the nasal fossae. The nodules at this time are not adherent to the underlying tissue. They do not bleed easily. Later they fuse to form a large granulomatous mass that encroaches upon the air passages. This mass of tissue has become adherent to the underlying tissue. Interference with breathing is then partial or complete, depending on whether the tumor mass fills one or both sides of the nares. The pharyngeal reflex is absent.

In the third stage, the granulomatous tissue enlarges and the patient acquires the appearance of a rhinoceros. Later as the lip becomes involved, he resembles a hippopotamus. Extensive mutilating ulcerations usually occur in the late stages of the disorder with the result that the palate becomes perforated and the bridge of the nose destroyed. The destructive process generally terminates with sclerosis of the tissues of the affected area, occlusion of the nasal fossae, strictures of the pharynx, and with involvement of the larynx and trachea.

The microscopic examination of material obtained from the affected areas reveals a dense infiltrate composed of three types of cells: plasma cells, v. Mickulicz cells and Russell bodies. The amount and character of the cellular infiltrate varies with the age of the lesion.

In the early stage of the disorder, the plasma cells are abundantly present in the dermis, particularly about the blood vessels. The plasma cells are separated from the epidermis by a thin zone consisting of lymphocytes mainly, with occasional polymorphonuclear neutrophils and histiocytes. A few reticulum fibers may be visualized with suitable staining methods.

In more advanced lesions, one sees moderate numbers of round, pale cells scattered throughout the plasma cell infiltrate. These are the v. Mickulicz cells. They are approximately 50 microns in diameter and possess a foamy, sketchy cytoplasm with a deeply staining eccentric nucleus. If a suitable stain is employed, many of them are seen to contain the Frisch bacillus. The majority of the v. Mickulicz cells undergo hydropic degeneration as a result of the extreme fragility of their cytoplasm.

In still more advanced lesions, the v Mickulicz cells occur in great profusion The Russell bodies, on the other hand, tend to disappear entirely although their number is not large at any time. These homogeneous, colloidlike elements without a nucleus are generally regarded as plasma cells which have undergone hyaline degeneration. The other cells of the granulomatous infiltrate disappear along with the Russell bodies.

In the late stages of the disorder the histologic picture is one of fibrosis The walls of most of the blood vessels have become sclerotic, resulting in marked narrowing of the lumina of these vessels. Degeneration of the collagen fibers and of the inter fibrillary ground substance occasionally takes place, representing the end stage of the scleromatous process

My associates and I in the dermatological department of the Rosales Hospital are of the opinion that the disease is due to a filtrable virus and not to the Frisch bacillus (Klebsiella rhinoscleromatis) The Frisch bacillus is found not only in the nasal secretions and histologic sections of material obtained from patients with this disorder but also in the nasal secretions of healthy persons This is especially so in those in whom the complement fixation test is negative. The disease has not been reproduced in laboratory animals.

The diagnosis is readily established by the typical clinical and histoanatomic appearances in countries where the disorder is endemic. The presence of dense infiltrates of plasma cells, v Mickulicz cells, and Russell bodies makes an unique histologic picture. Because of the granulomatous character of the lesions, the disorder should be distinguished from syphilis, tuberculosis, ozena, sarcoma, carcinoma, rhinosporidiosis, South American blastomycosis, and yaws with its complications of gangosa and goundou.

The disorder can only be eradicated if the diagnosis is established early

The mortality rate depends on whether the trachea is involved. If so, tracheotomy becomes a life-saving procedure.

The only effective treatment in my experience is with x-rays. Four series of seven exposures each are given during the first year This usually has to be repeated during the second and third years in patients with advanced lesions.

Each treatment consists of the following factors 200 Kilovolts. Filter 0.5 mm. copper and 1 mm. aluminum. Distance 50 cm. (20 in.) Dosage 200 r daily for seven consecutive days repeating this series every three months until four series have been given.

The use of sulfonamides during the intervals between x-ray therapy *is recommended. They should be administered intra muscularly*

Effective treatment with streptomycin has been reported by North American authors.

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American Mucocutaneous Leishmaniasis

By

Antonio Pena-Chavarria

THE FOLLOWING contribution is based on my experience with mucocutaneous leishmaniasis in various countries, particularly Columbia and Costa Rica.

The disease is popularly called papalomoyo in Costa Rica, where it has occurred endemically in certain regions for many generations. Papalomoyo is derived from the Aztec language and represents a combination of papalotl (butterfly) and moyotl (mosquito) This interesting derivation clearly indicates that the early inhabitants of my country well understood the predilection of the disorder for the central area of the face and suspected that the mosquito was concerned in its production.

Archaeologic findings of native pottery in the highlands of Peru attest to the antiquity of the disease. Linguistic and ethnologic evidence in support of this assumption is abundant. The Quechua Indians of Peru have named the type of mucocutaneous leishmaniasis characterized by involvement of the mucous membranes of the nose and mouth, uta, which signifies in their language, to gnaw

The sand fly or Phlebotomus is generally accepted as the intermediary host and vector of the causative agent of the disorder although other insects and certain plants probably play a role in the transmission of the infection. The sand fly abounds in highlands at an average elevation of 2300 feet above sea level, which is the area in which leishmaniasis occurs with the greatest frequency Sand flies are smaller than North American mosquitoes and can easily pass through the mesh of ordinary screens. One good thing about them is that they cannot fly very far

The disease is endemic in almost all Latin American countries, occurring at any time during the year but reaching its highest incidence with the onset of the heavy rains, which coincides with the season for planting and tree-felling Men engaged in such work, as well as in collecting chicle, are particularly susceptible, as they have the habit of taking off their shirts while working, thus presenting the sand fly with a large target for attack.

The disorder as it appears in the Americas is caused by two species of the genus Leishmania, L. tropica and L. braziliensis. They are morphologically indistinguishable in the microscopic examination of scrapings and cultures. The intradermal injection of leishmanin (reaction of Montenegro) produces equally strong reactions, no matter from which organism it is made. *L. braziliensis*, however has agglutinating properties *differing* from those of L. tropica, and methods of artificial immunization have not proved successful against infections with this species as they have against those caused by L. tropica.

The organism encountered in my experience in Costa Rica is morphologically identical with the causative agent of Oriental Sore and malignant mucocutaneous leishmaniasis occurring *in South America*. The parasite is present in great numbers at the edge of crust-covered ulcers. *After removing* the crust and swabbing the pus which covers the base of the ulcer superficial freezing of the area with ethyl chloride permits a painless scraping of the tissue directly under the edge of the ulcer This opens a way to the outer border of the encircling inflammatory zone *in* which one finds the greatest number of parasites. *It is best to discard the first two specimens because of* unavoidable contamination with pus The third specimen will usually be satisfactory providing it is not clouded with too much blood.

When tinted with Giemsa's stain, the leishmania color an intense red.

Both species appear intracellularly *in* tissue smears and *stained histologic preparations, eight or more parasites being* usually packed into a single histiocyte They appear as round or oval bodies, 2 to 4 microns in diameter each body having a nucleus and a tangentially placed kinetonucleus the situation of the latter serving to distinguish the various genera of trypanosomides

from each other The nucleus and kinetonucleus stain bright red and the cytoplasm, pale blue. The kinetonucleus produces the flagellum, when the parasite changes into the second phase of its life cycle in culture and in the digestive tract of the sand fly Extracellular parasites are occasionally found, attaining the size of 5 microns.

The incubation period was determined with a fair degree of accuracy in several residents of the city of San Jose, who spent three days hunting and fishing in known endemic areas. Initial lesions appeared in these men between 18 and 63 days after their vacation in the country However the possibility of a much longer incubation period should not be discarded.

A perusal of the pertinent literature reveals a certain degree of chaos in the classification of clinical types of the disorder The following classification is based on my experience with 350 patients with mucocutaneous leishmaniasis

1 Ulcerating type (cutaneous and mucocutaneous)
2 Vegetating or verrucous type.
3 Nodular type.

These three basic types are what I like to regard as evolutionary and clinical phases of the disorder The involvement of the mucous membranes of the nose and mouth as well as the dissemination of the ulcerating type through the lymph and blood vessels should be regarded as variants of localization occurring in patients with one or another of the three basic types.

The initial lesion is a vesicle or acuminate papule. The vesicle rests on an inflammatory base and rapidly enlarges to form a blister which contains a clear fluid. This is soon changed into pus. The blister breaks within a few days, disclosing a superficial ulcer with a red, granulating base and an elevated, hard border

The ulcer which forms at the tip of the acuminate papule occurs spontaneously or as a result of scratching It has the appearance of a craterlike furuncle and, like the ulcer following the vesicle, enlarges at the periphery

Ulcers developing from vesicles grow faster than those starting as papules attaining a size of 3 or 4 cm. in diameter within one or

two months. The elevated, red, inflamed border observed in fresh ulcers becomes lavender after a month. The inflammatory halo surrounding many of these ulcers disappears after two months. The thick, serosanguinous secretion from the base of the ulcer forms a crust which resembles the crust of pyogenic lesions occurring in patients with ecthyma.

Some of the ulcers increase in size to form lesions characteristic of the crusting, ulcerating type of the disorder while others dry up after two months or so and form pale red, papillomatous vegetations which later become verrucous.

In occasional instances, the papule does not ulcerate. Instead, it increases in size and assumes the appearance of a raspberry. Frambesoid lesions of this type are called figueria in Brazil and are frequently accompanied by multiple subcutaneous nodules along the course of the lymph vessels, as in sporotrichosis but differing from them in not usually suppurating. At other times, the initial lesion is a rounded nodule with a smooth, shining surface of normal epidermis without an encircling zone of hyperemia.

The initial lesion may occur on any part of the body the most frequent sites being the arms face and tip of the ear lobe. Unusual localizations in my experience were the scalp of one patient, the palmar surface of the hand of a six year old child, and the back of several farmers.

It is occasionally difficult to distinguish leishmanial ulcers of the legs from so-called tropical ulcers.

If the ulcers are not treated, more and more of the surrounding skin becomes involved. At the same time the ulcers deepen. They may remain limited to the skin, where they heal in time. However many persons having these ulcers develop ulcerating and mutilating lesions of the mouth, pharynx, nose, and external ear. When the hard palate becomes involved, its destruction along with that of the septum gives the nose a tapirlike aspect.

In three patients I saw perforation of the septum take place without subsequent mutilation. In two of these the soft palate was involved, with the formation of a livid patch dotted with yellow and red specks

In seven other patients, there was centripetal involvement of the lymph channels, dissemination of the infection apparently not taking place in the reverse direction. In most instances of lymphatic involvement, nodules form along the course of the hard, fusiform lymph vessels. The nodules soften in time and suppurate. Enlargement of the regional lymph nodes occurred in three patients with this type of dissemination.

In a patient with ulcers surrounded by a wide zone of edema, numerous papillomatous lesions suddenly broke out all over the body five months after the onset of the disease. The generalized character of the eruption with its acute onset made one think of an acute dissemination by the blood stream. However there was neither fever nor enlargement of the spleen.

The vegetating or verrucous form of the disorder does not tend to spread to the mucous membranes or through the lymph or blood vessels. Leishmania are not so abundant in this type of leishmaniasis as in the ulcerating type.

The nodular type of eruption does not ulcerate. The nodules remain covered with normal-appearing skin, except for the presence of some telangiectatic vessels. This type occurs very rarely and like the vegetating type does not become disseminated.

In patients receiving treatment, the ulcers rapidly dry up and lose their hard, inflammatory border The regrowth of epidermis starts at the edge of the ulcer and proceeds to the center, leaving a smooth, depigmented scar which remains depressed below the surface of the skin in patients in whom the subcutaneous fat and connective tissue have become involved. The infection may destroy underlying tendons and thus bring about extensive retractions of the scar

Histopathology Histologic sections of the ulcerating type of lesion show varying degrees of acanthosis. The dermis contains a diffuse infiltrate consisting mainly of lymphocytes and histiocytes. In early lesions, one sees a few polymorphonuclear leukocytes. The infiltrate is most dense in material obtained from the edge of the ulcer where the epidermis is still intact.

In the vegetating type, there is also a marked tendency to form keratotic centers and even horn cysts, resembling the keratotic

formations found in keratotic basal-cell epithelioma and squamous-cell carcinoma. Confusion with neoplastic disease however is impossible due to the absence in leishmaniasis of mitotic figures and anaplastic cells

The organism is present both within and without the cells of the infiltrate. It is not encapsulated, which helps to distinguish it from other organisms found in similar types of infiltrate.

Pathogenesis. The occurrence of the relatively benign vegetating type of the disorder chiefly in well nourished persons, leads me to believe that nutrition plays an important part in determining the course and type of infection. In patients showing signs of dietary deficiency particularly of protein, the disease is wont to run a malignant course with involvement of the mucous membranes of the mouth and nose leading to ultimate destruction of tissue.

On the other hand, persons in a good state of nutrition become only mildly affected, often throwing off the disease spontaneously

Immunology The Montenegro reaction is the most specific reaction of sensitization that I have encountered among the various protozoal and fungous diseases of the skin occurring in tropical America. It is more specific than the tuberculin reaction. The high degree of specificity of this reaction to intradermal leishmanin is displayed toward all species of Leishmania. The reaction has been positive in 96 per cent of the patients with leishmaniasis whom I have observed. It is of great diagnostic value in persons with long standing lesions suspected of being caused by Leishmania, but in which the organism cannot be found.

Treatment. The intravenous injection of tartar emetic constitutes the most effective and economical treatment of the disorder that I have found in over 25 years of experience. Treatment should be instituted as early as possible in the course of the disease using large doses for a long period of time. Recurrences are common when small doses are given at irregular intervals. For the same reason, the injections should not be stopped when the lesions have apparently healed.

The recommended dosage is 0 05 Gm of tartar emetic in the form of daily intravenous injections. Raising the dose to 0 1 Gm. is liable to bring on episodes of nausea, vomiting, joint pains and

neuralgia. The injections should be continued until a total of 2 Gm. have been given. This amount is usually sufficient, although it is occasionally necessary to give as much as 4 Gm. In general, it is better to give too much than too little.

If for some reason the patient cannot be given intravenous injections, the drug may be taken by mouth. In children, Fuadin is recommended, as it is given intramuscularly.

As adjuvant treatment, the local application of 5 per cent tartar emetic in an ointment containing zinc oxide and cod liver oil is highly indicated. In very early lesions, the sole use of this ointment has proved curative in many instances.

29

The Cutaneous Manifestations of Amebiasis, Chagas' Disease, and Toxoplasmosis

By

Frederick R. Schmidt

Cutaneous amebiasis. The parasite reaches the skin either by contiguity autoinoculation, or through the blood stream. The infestation of the skin manifests itself as a punched-out, irregularly spreading ulcer with raised and undermined edges. The base of the ulcer is composed of exquisitely painful granulation tissue covered over with necrotic debris and pus These ulcers have been reported occurring on the trunk, buttocks, legs, and around the anus. In a patient with proved amebic ulcer of the skin of the abdominal wall, the infestation was carried from the amebic focus in the intestine to the skin after an operation establishing an artificial anus.

The diagnosis rests on finding Endomeba histolytica in the ulcer which, when positive, separates it especially from pyoderma gangrenosum.

What shall we say about patients with intestinal amebiasis who have pruritus or urticaria at the same time? Is the amebic infestation a factor in the persistence of the cutaneous symptoms?

Borda and Casala answer this question in the affirmative They maintain that a wide variety of skin lesions are not infrequently due to toxins liberated by amebae living in the gastrointestinal tract and that they should therefore be regarded as allergic manifestations. While visiting Borda s clinic I had the privilege of examining a number of patients with intestinal amebiasis who had concomitant dermatoses usually associated with itching Effective treatment of the intestinal infestation led to cessation of itching and involution of the eruption in many of the patients.

The following plan of treatment for amebiasis was submitted by Dr Gonzalez Lujan.

The various symptoms caused by Endameba histolytica infestation consist, among others, of diarrhea, abdominal colic or distress, malaise, weakness, pain in the lower extremities, hyperhidrosis, headache, backache, joint pains, dysmenorrhea, cutaneous lesions, insomnia, and nervousness. It should be remembered, however that there is almost always a concomitant bacterial infection of the colon in patients with amebiasis and that this infection usually brings on its own train of symptoms. Consideration of the associated bacterial infection is important in treatment, since it appears that the amebae are more vulnerable when both bacteria and amebae are combated.

An acute attack may be either the manifestation of a recent infection or merely an exacerbation of an old one. In the acute attack, the predominant symptoms are diarrhea with or without tenesmus, abdominal pain, lightheadedness, or even fainting in severe cases.

The diarrhea should be controlled as soon as possible by the use of kaolin preparations, such as Kaomagma or Kaopectate, in doses of one tablespoonful every 15 minutes for several hours or longer if diarrhea persists and is severe. As an antidiarrheal coadjuvant in severe cases associated with abdominal pain and tenesmus, opium derivatives may be used. Of these, the plain tincture or camphorated tincture of opium are the most valuable- the former is given in doses of 10 to 30 drops and the latter in doses of one or two teaspoonfuls every two to four hours, depending on the severity of the symptoms. Severe diarrhea of this type associated with nausea and vomiting may require morphine.

The loss of electrolytes, water vitamins, carbohydrates, and proteins must be compensated as soon as possible. External heat to the abdomen affords comfort and relief of intestinal spasm.

In Dr Gonzalez experience, the most effective therapeutic agent in patients with either acute or chronic amebiasis is terramycin (oxytetracycline) administered in sugar coated tablets. The dose is 250 mg. four times daily for eight to 15 days or longer if the stools continue positive. After this course of treatment, stool examinations should be made every five to 15 days until

three consecutive negative examinations are obtained. The patient may then be considered cured.

The sulfonamides are useful in combating associated bacterial infection, one of the most effective being Formo-Cibazol (Ciba) which is given in the form of two to four tablets three or four times daily before meals for three to six days. After the bacterial infection has subsided, terramycin should be given in combination with Plewin (Winthrop)

In amebic hepatitis, abscess, or granuloma of the colon, terramycin has proved effective in doses beginning with two tablets four times daily for three days and then reducing the dosage to two tablets three times daily for three days, finally giving only one tablet four times daily for 15 days more. Improvement may be gauged by the decrease in size and tenderness of the liver as determined by the physical and x ray examinations as well as by the *patient s general condition.*

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Chagas disease or American trypanosomiasis. This disease is caused by Trypanosoma or Schizotrypanum cruzi and is carried principally from dogs, bats, armadillos, and opposums to human beings by the reduviid bug Triatoma.

Triatomas have substances in their saliva capable of producing sensitization phenomena in persons who have become sensitized by previous bites. Zeledon cites the instance of a woman developing widespread eruption of the body associated with headache, loss of appetite, nausea, and vomiting following the bite of T dimidiata. The patient occupied a house from which bugs were collected, and she gave a history of having had previous bites.

The conjunctiva and skin about the eye are common ports of entry for the parasite in infants and children, the disorder being more serious the younger the child Swelling of one lid usually sets in early although both lids are occasionally affected, while the conjunctiva becomes infected and edematous. The preauricular submaxillary and cervical lymph nodes on the affected side generally become painful and palpable, and the lachrymal duct

and ocular muscles may become involved as well. The edema of the lid and surrounding skin may last only a few days, but when it lasts for several weeks, it is replaced by a violaceous discoloration and a branny scaling

Various types of eruptions called chagasids may occur during the febrile stage, all of which tend to leave residual zones of brownish pigmentation. Chagasids are generally regarded as manifestations of hypersensitivity

Anasarca is met with occasionally being most marked on the face and legs It occurs especially in patients not showing evidence of a port of entry

The chronic stage may be associated with edema around the ankles due to myocarditis, for T cruzi is cardiotropic, and symptoms of cardiac involvement are sometimes the first and only evidence of chagasic disease.

T cruzi in fresh smears of parasitized human blood appears as a C or U-shaped trypanosome with an average length of 20 microns and has the characteristic morphology of all trypanosomes, including a centrally placed nucleus, a posteriorly located kinetoplast, and a flagellum. This form is present in the blood stream until *toward the end of the febrile period when the parasite invades* the tissues, in which it assumes a leishmanial structure.

Cystlike nests of these Leishmania are frequently found in the myocardium, in which they are surrounded by moderate inflammatory reactions. The nests break down from time to time and the round leishmanial bodies enter the blood stream to become again elongated trypanosomes.

T cruzi develops in Triatoma s intestinal canal, in which it finally assumes a trypanosomal structure and is expelled in enormous numbers in the fecal material during the act of feeding. It gains entrance to the human body through the mucous membrane the conjunctiva, a break in the continuity of the skin, or through the intact skin.

A definite diagnosis of early Chagas disease is made by the demonstration of the trypanosomal stage of T cruzi in the blood or by the inoculation of suspected blood into animals. For animal inoculation, Zeledon found the guinea pig and white mouse most useful and for cultivation of the organism from the blood, the Novy McNeal-Nicolle medium.

Xenodiagnosis as practiced in Costa Rica, is carried out by allowing clean, uninfected laboratory-bred, reduviid bugs to feed on the suspected patient. Two weeks later the contents of the hind-gut are expressed on a cover slip and examined for the presence of crithidia and particularly metacyclic trypanosomes.

Both Johnson and Zeledon found the complement fixation reaction made with an alcoholic antigen prepared from cultures of T cruzi highly specific.

The impression gained from the observation of patients in Costa Rica is that there is no cure for Chagas disease.

A child treated with aureomycin responded favorably at first with the disappearance of symptoms. A short time later after medication with aureomycin had been discontinued, the child reacted positively to tests demonstrating the presence of parasites in the body This observation is in accord with that of others and indicates that aureomycin not only fails to cure the disease but actually stimulates the production of parasites.

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Toxoplasmosis. The occurrence of this disease in adults concerns us because occasionally its onset is marked by an erythematous rash simulating that of Rocky Mountain spotted fever from which it differs however by sparing the palms, feet, and scalp.

The intracellular nature of the causative organism T gondi, in the reticuloendothelial system is somewhat similar to that of the etiologic agents of leishmaniasis and histoplasmosis.

Labile toxoplasma neutralizing antibodies are sometimes present in the blood, but lysins, precipitins and agglutinins have not been demonstrated in the sera of infected persons.

No satisfactory treatment has been developed, although the sulfonamides exert a suppressive effect on T gondi.

30

The Pigmentary Dermatoses

By

Luis E. Pierini

Pigmentary dermatoses constitute a large group of disorders characterized mainly by uneven distribution of pigment. The pigment may be normal, like melanin or hemosiderin, abnormal, like bilirubin or carotene; or artificial, like heavy metals or hydrocarbons.

PRIMARY MELANODERMA

Adult forms of primary hyperpigmentation resulting from:

Cryptogenic factors	Ochronosis, hemochromatosis
Metal poisoning	Argyria, chrysiasis, bismuthia, chronic arsenical poisoning
Endocrine disturbances	Addison disease, acanthosis nigricans
Deficiency diseases	Vagabond' disease, senile cachexia, pellagra
Acute hemosiderosis	
Systemic infections	Syphilis, malaria, etc.
Occupational factors	Lichenoid melanodermatitis, argyria
Disturbances of the liver	
Nevoid growths	

Infantile forms of primary melanoderma:

Incontinentia pigmenti, congenital melanoderma, bullous keratogenous and pigmentary dermatitis with blood eosinophilia

The pigmentary dermatoses considered in this article may be divided conveniently into generalized and circumscribed melano-

derma, the latter being better designated as melanosis. I shall not discuss nevi, tattoos, and similar small, localized pigmented lesions.

Diffuse melanoderma may be classified as primary and secondary depending on whether hyperpigmentation is the first evidence of cutaneous involvement, or whether it follows a skin disease such as papular urticaria or dermatitis herpetiformis.

PRIMARY MELANODERMA

Ochronosis is a rare disorder characterized by a generalized bluish-black pigmentation of certain areas of the skin, dark-colored urine, and often osteoarthritis. It affects the middle-aged and may be hereditary

The skin of the nose, knuckles, thenar and hypothenar eminences is most heavily involved, although the cheeks, lips conjunctivae, buccal mucosa, ears neck, chest, and extremities appear various shades of gray-brown and black. Nodules may occur on the ears. There are pigmentation and hardening of almost all cartilage. The viscera are usually involved, with the exception of the liver Pigmentation of the cornea and sclera may stimulate malignant melanoma.

Osteoporosis and sclerosis, together with calcification of the intervertebral discs and tendons may be extensive. Osteoarthritis of this type may bring about spontaneous fracture and fixation of joints

These changes force the patient to walk slowly in a stiff humpbacked manner with his head forward, his feet wide apart, and his arms hanging stiffly at his sides.

The urine appears normal when voided, but it quickly grows dark due to the presence of a reducing substance, hemogentisic acid. Of diagnostic value therefore are darkly-spotted underdrawers. Ochronosis however may also occur without the presence of hemogentisic acid in the urine

In histologic sections, the epidermis appears normal. The pigment is located in the dermis where it displaces the normal connective tissue. It appears as round or oval conglomerates or diffusely scattered throughout the dermis. It does not color with routine stains for melanin.

Ochronosis is caused by the incomplete degradation of tyrosine, whose oxidation stops with the formation of hemogentisic acid, due to lack of the enzyme required for its further degradation. The reason for the predilection of the disorder for cartilage is unknown.

Hemochromatosis, or **bronze diabetes**, is a rare disorder affecting mainly middle-aged men, particularly alcoholics. Its familial and hereditary origin is based on a congenital defect of iron metabolism.

The disease is a syndrome consisting of disturbances of the liver and gall bladder tract, together with abnormalities of hemosiderin distribution and glucose metabolism. The skin of the face, back of the forearms and arms, external genitalia, nipples, and knuckles is most deeply pigmented.

There may be symptoms of infantilism, associated with loss of libido blood dyscrasia, hypotension, and cardiac insufficiency

In histologic sections, the epidermis and dermis appear normal, except for the deposits of hemosiderin. Particles of hemosiderin are found around the small blood vessels and within melanophores in the upper dermis as well as in the membranae propriae of the sweat glands. The epidermis occasionally contains hemosiderin. With suitable stains one sees evidence of increased melanin pigmentation in the basal cells and dermal melanophores. Occasionally the iron pigment disappears from the skin, and only melanin remains.

The prognosis in patients with hemochromatosis is unfavorable, although the process can be held in check with the use of suprarenal extract or ascorbic acid.

Argyria and **bismuthia** are rapidly becoming medical rarities, due to the decline in medical use of silver and bismuth salts. Middle-aged women develop argyria slightly more frequently than men, melanoderma usually appearing two years after the patient started taking a preparation containing silver for relief of indigestion or instilling protargol or argyrol into the vagina or urethra.

The pigmentation in argyria involves only the exposed parts of the skin, the affected areas appearing bluish-gray or slate-colored.

Although routine stains may be used, the best method for the demonstration of silver in histologic sections is by dark field illumination. The deposits of silver granules are densest in the basement membranes surrounding the sweat glands and the papillary portion of the dermis. Lesser numbers of granules are found in the homogeneous basement membranes of the small blood vessels, sebaceous glands and hair follicles.

Chrysiasis may occur following the parenteral use of gold salts. The skin of exposed areas appears grayish-blue or yellowish-brown, particularly when associated with subsequent exposure to sunlight or ultraviolet light. The covered parts of the skin also contain gold deposits which can be demonstrated spectroscopically

Women with light complexions who are around 35 years of age are especially predisposed to this type of pigmentation, depending on the type and quantity of gold administered.

In histologic sections, the epidermis appears normal. Gold granules are best demonstrated by histochemical methods and microincineration. The granules usually lie within histiocytes and endothelial cells of the capillaries and lymph vessels, and occasionally they are scattered throughout the dermis. The gold deposits disappear from the skin in time.

Hyperpigmentation occurs in patients with chronic arsenical poisoning due either to inorganic arsenical preparations or water with a high arsenical content. Water containing more than 0 0005 mg. per thousand of disodium arsenite is considered unsafe. Occupational arsenical pigmentation is not infrequent.

Middle aged white men are more frequently affected than women. The pigmentation usually follows a succession of gastrointestinal and nervous symptoms. Keratoses then develop, followed by areas of erythema and later hyperpigmentation. The pigmentation starts as tiny spots on covered areas of the skin and spreads by coalescence It is associated with scaling, keratoses, and in some cases, dilated blood vessels and atrophy

The lesions tend to develop into squamous-cell carcinoma after passing through phases of dyskeratosis in which the cells may show changes observed in Bowen s and Paget s diseases.

Addison s disease is characterized mainly by weakness, low blood pressure and partial or generalized pigmentation of the

skin. The pigmentation first appears on the knuckles, from which it spreads to areas of the skin normally darker in color as the flexural surfaces in the axillae, groin, and about the nipples. The skin feels soft. The mucous membranes of the mouth, anus vagina, and the skin of the hands and face ultimately become pigmented. The skin about the eyes, mouth, and nails is the last to be involved. The hair usually turns gray and falls out. Hyperhidrosis may be pronounced.

In histologic sections of the skin, there is no evidence of atrophy or degeneration. The melanin is deposited in the basal cells of the epidermis and in the tips of the interpapillary pegs where it appears in the form of caps above the nucleus. With silver stains, one sees a few dendritic cells and a moderate number of melanophores laden with melanin.

Addison's disease is currently regarded as an expression of faulty adaptation by the adrenal glands to environmental and emotional stress. The associated depletion of adrenal corticoids can be remedied by the administration of adrenal cortical extract, the cortisones, and re-establishment of sodium and potassium equilibrium.

Acanthosis nigricans is characterized by verrucous, hyperpigmented patches occurring most commonly in the axillary and genital regions, buttocks, on the neck, inner aspects of the thighs, and about the mouth. The disorder may start with itching and pigmentation, together with a dry tongue. The affected skin appears dirty-gray or brown, the color merging gradually with that of the surrounding skin.

Papillomatosis is expressed clinically by a dry smooth, thickened, and furrowed skin, from which the wrinkles do not disappear when the skin is stretched. Wherever the skin is dry the lesions tend to become shiny Solitary papillomas occasionally grow so large that they resemble hair

Two types are recognized, one called malignant because it is associated with visceral cancer particularly of the stomach, and the other benign because it occurs without this association. The cutaneous changes usually appear from one to five years before the development of internal cancer although occasionally the opposite occurs, as in a patient of mine in whom hyperpigmented patches appeared years after surgical removal of the cancer The

occurrence of lymphosarcoma with metastases to the skin and subcutaneous tissue has been reported.

The benign form appears to be familial, affecting short, stout girls before puberty. They usually present a large number of soft fibromas on the neck and under the arms.

The histologic examination reveals the cells of the basal layers laden with melanin, particles of which can often be seen as far outward as the horny layer. The papillae are greatly increased in number and size, projecting upward as pegs covered with a moderately thickened rete malpighii and slightly thickened granular layer. Horny material fills in the gaps between the papillomatous pegs. A moderate amount of edema and inflammatory infiltrate, together with melanin-laden melanophores and scatterings of melanin, are usually found in the dermis.

Vagabond's disease associated with hyperpigmentation occurs mainly in impoverished old men infested for a long time with body lice. The initial urticarial papules provoked by the parasite localize wherever the clothes press or bind the skin, as on the upper back, stomach, lumbar region, and front of the thighs. Scratching results in the formation of linear excoriations and crusts, leading ultimately to patches of lichenification and thickening of the skin of the entire body.

The skin in these patches becomes dry, rough, scale-covered, and deeply pigmented, and often shows evidence of infection. Scattered throughout these areas of pigmentation are many white scars resulting from scratching. Itching is not periodic, although it is less at night because the bed linen is less infested than the clothing worn during the daytime.

Systemic reactions may occur in rare instances. Whether they are caused by endotoxins excreted by the louse, by associated vitamin deficiencies or hepatic disturbances, or some other factor is unknown. The occurrence of pigmentation of the lips speaks in favor of an etiologic factor other than scratching.

The skin tends to whiten in time, providing the patient does not return to his former life of vagabondage.

The pigmentation occurring in senile cachectic persons is evidence of general ill health.

In pellagra, after a prodromal period, during which the patient

complains of weakness, dizziness, diarrhea, and other symptoms, cutaneous lesions appear on exposed areas, such as the face, back of the hands, wrists, V area of the chest. The skin first becomes red and later dirty-gray thickened, and scaling. Hyperpigmentation occasionally takes place in areas not exposed to sunlight.

Pellagra affects chiefly men between 30 and 60 years of age who are habitual drinkers of quantities of denatured alcohol and who eat very little nourishing food. The disease is a manifestation of multiple vitamin deficiency particularly of nicotinic acid. The combination of heavy drinking and exposure to sunlight is definitely a precipitating factor

If the specimen for biopsy is taken from an advanced lesion, one will see areas of hyperkeratosis, parakeratosis vacuolization of the cells of the rete malpighii, and increase in the amount of melanin in the cells of the basal layer Later there is degeneration of the collagenous and elastic fibers, and the nerve fibers become thickened and show beadlike constrictions.

Treatment with the amide of nicotinic acid, polyvitamin preparations, and liver extracts together with abstinence from alcohol and use of sun-screening ointments has proved rapidly effective in my experience.

Acute hemosiderosis is the provisional designation of the disorder described independently by me and others. The disorder affects adults over 20 years of age at any time of the year and without evidence of visceral involvement.

Acute hemosiderosis starts on the legs and spreads rapidly to the buttocks, back, and shoulders possessing all the features which we associate with progressive pigmentary dermatosis. An additional feature observed in acute hemosiderosis is the tendency to rapid enlargement displayed by lesions occurring on the legs buttocks, lumbar regions, and areas behind and in front of the armpits. Areas of erythroderma may occur associated with intense itching. In the average case, however itching may be present only in the early stages of the disorder

The initial lesions consist of tiny dark red, scale-covered, punctate papules resembling grains of cayenne pepper which upon involution leave patches of pigmentation persisting for a year or more. The histologic sections show an increase in the

number of capillaries in the upper dermis the walls of which show inflammatory changes. Deposits of hemosiderin are present in the dermis. The epidermis is normal in appearance.

The use of vitamins C and K by mouth and rutin by injection proved effective in patients under my care

Syphilis is only rarely associated with pigmentation, the cause of the pigmentation being attributed to syphilitic involvement of the adrenal glands. Although this involvement is generally regarded as taking place during the secondary stage of acquired syphilis, I have seen the development of generalized pigmentation in a patient who had long passed the secondary stage. This patient had aortitis, hypertension, and a positive Khan reaction of the blood.

Malarial patients in advanced stages of the disease have an ash-gray discoloration of the face due to the deposition of hemosiderin and the specific pigment elaborated by the parasite.

Lichenoid melanodermatitis, which is called tar melanosis in the United States, occurs particularly in workers handling pitch or tar of various types and involves the skin of the face, sides of the neck, forearms, and hands. Avitaminosis and sunlight are usually regarded as precipitating factors in the production of this disorder

The pigmented areas appear dirty violet or black and occur as solid or reticulated patches, often deeply pigmented along the course of the veins. In addition to hyperpigmentation, follicular pustules may form on the arms associated with inflammation and itching The occurrence of bullae on the knuckles is not infrequent. Areas of lichenification may result from scratching.

The pigmentation may persist for a long time after the disappearance of lichenification and folliculitis. The patient must quit his job in order to get well.

Disturbances of the liver undoubtedly play an important part in the production of hyperpigmentation although experimental evidence in support of this contention is not conclusive. It is therefore advisable to make tests for liver function in patients presenting pigmentation of the skin before going on to search for other possible etiologic factors

Congenital melanoderma is an anomaly of extreme rarity Two sisters whom I observed showed symmetrically placed areas of pigmentation involving the skin of the front of the legs, knees, buttocks forearms, shoulders, and back of the hands. The affected areas appeared dark-chestnut, growing more yellow as the pigment deepened and spread to other areas. Systemic symptoms and blood changes were absent. The histologic sections showed greatly increased melanin-deposition in the cells of the basal layer of the epidermis and in a few melanophores.

Incontinentia pigmenti is an inborn anomaly characterized by irregularly shaped, disseminated patches of pigmentation limited to the trunk. The earliest lesions appear in the first few days of life in the form of linear vesicles on a reddened skin, usually associated with itching Months later linear verrucous lesions resembling linear nevus make their appearance, after which the skin becomes pigmented in the form of bizzare whorls with spidery fingers. The disorder subsides after a few years, usually leaving a normal skin. Occasionally however the child is left with a residue of scars and reticulated areas of atrophy resulting from lesions occurring in the initial inflammatory stage.

The disorder is usually associated with other congenital dysplasias of the skin and eye. It is apparently caused by the inability of the basal cells to hold melanin, which becomes more than slightly soluble in the fluid produced by vacuolization and subsequent rupture of some of the basal cells.

In histologic sections, many of the basal cells show vacuolization. The pyknotic nuclei are pushed to the upper edge of the cell. The amount of melanin in the basal cells is normal. In the upper dermis, the melanophores are packed with melanin, and even the perithelial cells surrounding the capillaries contain particles of melanin.

SECONDARY MELANODERMA ASSOCIATED WITH

Generalized exfoliative dermatitis	Baccaredda type, idiopathic, prurigo of Hebra, Norwegian scabies, etc.
Prurigo	Melanotic prurigo chronic prurigo with lichenification
Lichen planus, dermatitis herpetiformis, pemphigus foliaceus, impetigo herpetiformis, scleroderma, dermatomyositis, poikiloderma	

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SECONDARY MELANODERMA ASSOCIATED WITH

Generalized exfoliative dermatitis	Baccaredda type, idiopathic, prurigo of Hebra, Norwegian scabies, etc.
Prurigo	Melanotic prurigo, chronic prurigo with lichenification
Lichen planus, dermatitis herpetiformis, pemphigus foliaceus, impetigo herpetiformis, scleroderma, dermatomyositis, poikiloderma	

Bullous keratogenous and pigmentary dermatitis with blood eosinophilia is closely allied to incontinentia pigmenti. The eruption occurs exclusively in newborn girls a few days after birth in the form of papules, vesicles bullae, and pustules localized mainly on the legs Stripes of verrucous keratoses then form, the disorder finally healing with scars and areas of pale brown pigmentation. Severe eosinophilia is associated with the vesicular phase. The outstanding lesion is the warty keratosis, not hyperpigmentation.

Generalized exfoliative dermatitis, regardless of whether it occurs as an idiopathic disease or as a complication of other cutaneous disorders, is with few exceptions associated with hyperpigmentation only in the terminal stages of fatal cases.

One of these exceptions is a form of exfoliative dermatitis described by Baccaredda as benign hyperplastic cutaneous reticulohistocytosis associated with hyperpigmentation. The disease affects persons over 50 years of age. It usually starts with patches of erythema which fuse and in the course of a few weeks cover the *entire cutaneous surface* There are considerable edema and infiltration of the skin associated with scaling and itching Occasionally the disease manifests itself with the appearance of keratoses on the palms and soles, upon which redness supervenes. The lesions may become eczematized or purpuric, in which case residual pigmentation may persist for many months finally shading off without disappearing completely The mucous membranes *are not involved. Ectropion occurs in most patients* with the disorder

The course of the disease is slowly downward, the patient growing progressively weaker and emaciated, until death occurs as a result of intercurrent infection or complicating disease.

The hemogram shows *a slight drop in the* number of red blood cells. At first, the leukocytes are normal in number and appearance Later there is leukocytosis with a great increase in the number of large reticular and monocytic cells at the expense of neutrophils. The large cells have nuclei of varying shape some being round and others either club or kidney shaped. Both spinal fluid and material obtained from lymph nodes show the

same type of cell resembling the large, immature reticulum cell seen in mycosis fungoides.

Patients with acute prurigo, which is called papular urticaria by English-speaking dermatologists, usually do not show pigmentation of the skin. This is also the case in prurigo nodularis, actinic prurigo, and neurodermatitis. The discoloration seen in patients with prurigo of Hebra, or the generalized forms of prurigo associated with lichenification, is caused by almost constant scratching.

There is a type of prurigo, however, of which the most striking feature is the pigmentation. This is melanotic prurigo, described by Borda and me, which affects mainly women. The pigmented areas are limited at first to the shoulders, back, deltoid region, and under the breast, the lesions being symmetrically placed. They may fuse and become generalized. Itching is intense in the affected areas. Small, round, brown papules soon make their appearance. In older areas of pigmentation, one sees whitish scars resulting from scratching.

Patients with melanotic prurigo invariably show serious disturbances of liver function, occasioned by cirrhosis in some instances. Cirrhosis of the liver caused hypercholesteremia and xanthomatous lesions of the skin in two patients.

Histochemical studies show that the pigment is melanin.

Treatment should be directed against the associated hepatic insufficiency.

The pigmentation seen in the healing phase of lichen planus occurs at the site of the initial lesion. The color of these areas is slate-gray or shades of gray. The mucous membranes also become pigmented. Arsenical and aural lichenoid eruptions usually leave extensive residual pigmentations which persist for a long time.

Dermatitis herpetiformis has a well-defined symptomatology which is universally recognized. The residual pigmentation seen in patients with this disorder is so characteristic that the diagnosis can be made on this feature alone. This is particularly valuable in the diagnosis of atypical varieties undergoing involution and in the distinction from pemphigus vulgaris, which is never associated with residual pigmentation.

The color of the pigmentation is sooty-brown. I believe that, together with the occurrence of bullae, pigmentation constitutes the salient feature of this disorder which unfortunately is not emphasized in the literature.

Patients having pemphigus foliaceus may show intense pigmentation during the phase of generalized exfoliative dermatitis following the earlier eruptive phase of bullous formation. The occurrence of pigmentation in these patients indicates a favorable prognosis.

Impetigo herpetiformis is a rare disease occurring mainly during the second half of pregnancy. It may also affect men and women showing symptoms of hypoparathyroidism following operations on the thyroid gland. The lesions encountered in this disorder are pustules set in groups on erythematous patches in the genitocrural region and other intertriginous areas. The pustules may fuse and give rise to widespread exfoliative dermatitis. On removal of the sticky heavy crusts, one finds a moderate amount of residual pigmentation which requires a long time to fade out.

The pathogenesis is clear in patients with frank symptoms of hypoparathyroidism. In pregnant women, it is believed that a latent state of congenital hypothyroidism is activated by pregnancy.

The treatment of choice in cases due to hypoparathyroidism is the use of dihydrotachysterol.

MELANOSES

Primary	*Secondary to*
Chloasma	Injury: Friction, rubbing, scratching
Riehl's melanosis	Physical factors: Burns, frostbites, ultraviolet, actinic, X-ray and radium irradiation
Phenolic melanoses	Chemicals: Toilet water, face creams, caustics
Poikiloderma reticulare	Dermatitis medicamentosa: Antipyrin, pyramidon, phenolphthalein, etc.
Atrophic and degenerative melanoses	Infectious agents: Fungi, pyogens, etc.
Nevoid melanoses	

In scleroderma, dermatomyositis, and poikiloderma, there often is coincident pigmentation during the earlier phases of the disorder In scleroderma, pigmented patches may be large and widely distributed, while in dermatomyositis they are reticulated and limited to the skin of the neck, face, and shoulders, tending at times to become generalized. Large, reticulated patches with telangiectases and areas of atrophy are features of poikiloderma.

The pigmentation in chloasma is commonly limited to symmetrical areas of the face occurring particularly in pregnant women. The color of the affected areas varies from a slight staining of the skin to a deep yellow or yellowish-green. The discoloration has well-defined margins. Chloasma is an example of an uncomplicated dyschromia, since it is not associated with scaling or atrophy Different types of chloasma are recognized, depending on the localization and whether it affects men or nongravid or pregnant women.

There may be a familial tendency toward chloasma. Five members of a family recently consulted me because of patches of localized pigmentation on their faces. Sisters and brothers were equally affected.

Seborrhea may act to fix the discoloration.

Correction of coincident endocrine or uterine disturbances is indicated *The internal use of vitamin C and other remedies has* proved disappointing in my experience, while the topical application of hydrophylic ointments containing 20 per cent of monobenzolester of hydroquinone (agerite alba) is quite effective. Iontophoresis with 20 per cent ascorbic acid is equally satisfactory

Riehl's melanosis begins with symmetrically placed areas of redness and swelling, upon which scaling supervenes. There is coincident itching After a few months, during which time the patient has repeatedly applied a harmful facial powder or other cosmetic, the redness and swelling give way to hyperpigmentation. The color of the pigmentation varies from a clear gray to a shade between chocolate and old bronze. It is commonly limited to the face and occasionally also to the neck and chest. The pigmented patches are darkest in the center, from which the

color grows lighter toward the periphery where the pigment breaks up to form small islands of discoloration.

The disorder often occurs in men and women employed in various occupations which do not oblige them to be exposed to sunlight. It was formerly believed that persons showing this type of pigmentation had become sensitized to sunlight through eating bread deficient in vitamins.

In a study of several hundred cases, I was able to show that the pigmentation is due to the use of cosmetics containing tar or its derivatives All patients with this condition were women with dark complexions, the majority of whom were between 30 and 50 years of age. Often there were coincidental menstrual irregularities. An allergic background was usually present.

The causative agent was shown to be Orange II, an aniline stain obtained from the fractional distillation of crude coal tar The dye was usually incorporated in facial powders.

In histologic sections, one sees scattered areas of hyperkeratosis surmounting a thin granular layer and rete malpighii. The number of clear cells is increased. The cells of the basal layer usually contain an increased amount of melanin. Some basal cells however are vacuolated and do not contain melanin. The upper portion of the dermis shows large numbers of melanophores Some specimens show a moderate inflammatory infiltrate surrounding the capillaries

Riehl's melanosis has practically disappeared in the last few years due to the superior quality of cosmetics

Erythrose pigmentaire peribuccale is an uncommon form of Riehl's melanosis in which the pigmentation occurs about the mouth and extends over the chin and along the nasolabial folds.

Melanosis is likewise produced by the use of facial creams containing resorcin or lenigallol, both of which are phenolic derivatives. The color and configuration of the pigmentation produced by these substances vary greatly

Poikiloderma reticulare of Civatte is a melanosis occurring in middle-aged women. The pigmentation has a reticular arrangement and is localized on the neck and face. The patches of discoloration are traversed with a network of telangiectases. *There* is a certain tendency to symmetrical *distribution* of the *lesions as*

well as a tendency to spare the center of the face and median zone of the neck.

The pigmentation appears bluish-brown on the forehead, where it forms a solid band. On the neck, the pattern of telangiectatic vessels is pronounced, and the mixture of the dusky color of the pigmentation and the red of the blood vessels imparts a characteristic tint to the lesions.

The histiologic appearance of poikiloderma reticulare simulates that of Riehl's melanosis.

In my opinion, the disorder represents a manifestation of light sensitization induced by menopausal or uterine disturbances.

The disorder persists for quite a while until it finally disappears spontaneously.

Atrophic and degenerative forms of melanosis represent advanced lesions of poikiloderma reticulare. The worsening of the lesions of poikiloderma reticulare results from such various factors as sunlight, senility and sudden loss of weight.

Pigmented nevi may at times assume an unusual configuration, occurring as round or bandlike patches of dusky pigmentation mixed with shades of yellow and green. The nevi may appear during childhood or late adolescence. Treatment is of no avail in stopping the steady extension of the pigmentation to other areas of the body.

The secondary melanoses represent pigmentations resulting from rubbing, scratching, burns, frostbites, caustics, perfumes, and ointments. Furthermore, the skin may become pigmented from the action of pyogenic organisms, fungi, x-rays, radium, or ultraviolet light. The localization of the lesions and the history of the case usually point to the correct diagnosis.

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Epithelial Nevi Exclusive of Melanoma

By
Marcial I. Quiroga

EPITHELIAL nevi are tumors of the surface epidermis and of the epidermal appendages, in which nevus cells may or may not be present. Like all nevi, epithelial nevi originate during fetal life as a result of a modification imposed upon the embryonic cell by a diffusible substance having the properties of a sterol. This substance is transmitted from cell to cell and thus controls the development of a group of cells composing a particular organ or part of it. This phenomenon of modification of the embryonic cell is called induction, and it is acted upon environmentally by mechanical, physical, toxic, and infectious agents during intra uterine life and after birth by biologic factors associated with puberty, menopause, and senility

Nevi may therefore be apparent at birth or develop at any subsequent time. In contrast with the genodermatoses, which are genetically induced, nevi are not familial.

It is difficult to find an adult person without at least one nevus. In an analysis of 741 cases of epithelial nevi, Becker found the following localization

LOCALIZATION OF EPITHELIAL NEVI (BECKER)

Localization	*No of cases*	*Percentage*
Scalp	15	2.00
Face	303	40.90
Neck	77	10.39
Trunk	190	25.65
Upper extremities	33	4.45
Lower extremities	49	6.61
External genitalia	4	0.54
Localization not given	62	8.36

Epithelial nevi are characterized histiologically by hypoplasia or hyperplasia of epithelial cells limited to circumscribed areas of the epidermis. The hypoplastic or aplastic nevi persist as such indefinitely and do not tend to grow or undergo malignant neoplasia, while the hyperplastic nevi which may contain nevus cells or "nevocytes" maintain their growth-potentiality throughout life, not infrequently becoming more differentiated as well as malignant.

If induction is imposed on highly differentiated cells, the resulting nevoid growth will be monodysplastic, i.e., it will, for example, be either a pigmented mole or a hairy mole. If, however induction acts on immature, pluripotential cells the resulting nevus will be polydysplastic, i.e., it will, for example, be a pigmented and hairy mole or a hairy pigmented warty mole.

Depending on the part of the epidermis affected and the presence or absence of nevocytes, nevi resemble the matrix from which they develop. Thus there are verrucous, papillomatous, cellular pigmented, depigmented, hairy and glandular nevi.

1. **Nevus verrucosus.** Synonymy: hard nevus, linear nevus wartlike mole, nevus unius lateralis, keratotic nevus, epidermal nevus, and ichthyosis hystrix.

The verrucous nevus is a circumscribed, round, warty growth of brownish or blackish color occurring singly in groups, or in continuous or broken-up streaks, bands or patches which often have a bizarre pattern. The individual element varies in size from that of a lentil to areas involving a large part of the cutaneous surface. The bathing-trunk variety of systematized verrucous nevus is representative of this widespread involvement. Depending on the surface consistency there are lichenoid, psoriasiform, ichthyosiform, and follicular varieties. This type of nevus does not tend to become malignant.

Histologically there are hyperkeratosis and acanthosis of varying degree. Hyperpigmentation of the basal cells is also present. A slight perivascular inflammatory infiltrate is found in the dermis.

The verrucous nevus may be destroyed by the electric cautery or fulguration.

2. **Nevus papillomatosus.** The most representative nevus of this type is the senile wart or seborrheic keratosis. It begins as a

The situation in lentigo maligna is entirely different and will be discussed by Dr Becker

4. Nevus depigmentosus. This nevus appears in two forms. *As nevus anemicus, it is manifested as a milky white macule* with a smooth surface The benign nature and slight cosmetic disfigurement of this birthmark require nothing more than a prescription for an efficient skin-colored cream.

5. Perinevic vitiligo or leukoderma acquisitum centrifugum is a condition in which each of the small, round, clear patches has a brown mole at the center The trunk and extremities are the sites of predilection. Perinevic vitiligo usually persists for a long time. Occasionally however pigmentation takes place following the spontaneous disappearance of the central brown mole It is not clear whether this condition is a variety of vitiligo or a manifestation of inhibition of pigment formation caused by the presence of the centrally located brown mole.

Treatment consists in destroying the brown mole by the electric cautery or fulguration or in excising it with the knife, either procedure sometimes being followed by pigmentation of the encircling clear halo.

6. *Nevus Pilosus. It was previously pointed out that* cellular moles are sometimes covered by a few or more black, thick hairs. In addition to this type of hairy mole cutaneous areas of varying size and shape may be covered with a hairy growth which in rare instances embraces the entire integument and, when associated with pigmentation, gives the person the appearance of a monkey

7 Nevus glandularis. Among the glandular nevi it is customary to include the sebaceous adenomas and the hidradenomas.

Adenoma sebaceum appears both symmetrically and asymmetrically The symmetrical sebaceous adenomas may conveniently be *divided into the following three types*

1 The Pringle type manifests itself as numerous reddish or yellowish brown small soft papules occurring mainly on the face. *On histologic examination* one sees a circumscribed growth consisting mainly of horn cysts numerous mature sebaceous glands, and conglomerates of basal cells The minute blood vessels of the upper dermis are dilated. From this it is evident

that it is erroneous to apply the term adenoma to the condition described by Pringle, since the sebaceous glands are not adenomatous but merely present in large numbers.

2. In the Balzer type the lesions have the color of normal skin. Histologically there are hyperplasia of the sebaceous structures, degeneration of the hair follicles, and large cell masses which contain cystic spaces in the center This type is synonymous with tricho-epithelioma.

3. The Hallopeau Leredde-Darier type is a true adenoma. It is characterized by small, slightly raised nodules having the color of normal skin, occurring mainly on the face and neck. In contrast with those of the Pringle type, the papules of this variety of sebaceous adenoma are hard and fibrous Histologically the papules reveal themselves as made up of fibrotic connective tissue and lobules of sebaceous cells, so that the histologic picture closely resembles that of true sebaceous adenoma.

The asymmetrical sebaceous adenomas may be divided into the following forms

1. Nevus follicularis. This condition is confined to the neck and upper part of the chest and arms and is characterized by the presence of raised or depressed, greasy comedolike lesions appearing singly or in groups. The lesions may become acneform, in which case one finds epidermal cysts, abscesses, or fistulae situated in small patches of pigmented skin. Histologically there are small localized epidermal invaginations going deep into the dermis or lying parallel or tangential to the surface epithelium.

2. Senile sebaceous adenoma or nevus. This condition occurs in persons past middle age in seborrheic areas such as the face, neck, scalp and back, as one or several small, flat yellowish, pinhead-sized and larger nodules. The surface of the lesions is often lobulated as a result of the coalescence of several enlarged sebaceous glands. These growths are composed of large numbers of hypertrophic mature sebaceous glands. The normal function and structure of the sebaceous gland are preserved. The growths may be destroyed by fulguration.

3. Fordyce's disease. This condition is manifested by the presence of solitary or grouped tiny yellowish, rounded spots on the vermillion of the lips, the oral mucosa, prepuce, glans penis

and vulva. The presence of hypertrophic mature sebaceous glands in regions where they are usually absent permits us to classify Fordyce's disease as a hamartoma. The spots may be removed by fulguration.

4. Nevus sebaceus (Jadassohn). Synonymy: progressive sebaceous adenoma (Darier) and nevus epitheliomatosus (Frieboes).

Sebaceous nevus appears as a solitary, raised, yellowish patch with a warty, lobulated surface and irregular shape. It arises during infancy on the scalp or face, and when located on the scalp it causes loss of hair at the site of the lesion. The growth is made up of hypertrophic, mature sebaceous glands. Destruction by the electric cautery or fulguration is completely satisfactory.

Hidradenoma. Synonymy: syringoma, syringocystadenoma, syringocystoma, and lymphangioma tuberosum multiplex.

These small and benign nevoid growths are only important from a cosmetic standpoint. They are not adenomas, since they are composed of minute cysts representing enlarged sweat ducts filled with hyaline material.

The so-called eruptive hidradenomas are small, soft, skin-colored or pinkish, rounded or flat nodules with a smooth surface occurring in crops mainly in young women on the chest and upper arms. The lesions are painless.

Confusion occasionally arises between these growths and the lesions of lichen planus or papular syphilis.

The occurrence of hidradenomas on the eyelids, particularly the lower lid and the adjacent skin just beneath the eye in elderly women with a tendency to a wrinkled skin, offers confusion with tricho-epithelioma. These circumorbital hidradenomas are slightly smaller and more irregularly shaped than those occurring elsewhere on the skin.

Histologic examination of the hidradenomas reveals numerous solid strands of epithelial cells and small, cystic ducts in the upper part of the dermis. The ducts do not communicate with either the epidermis or the sweat glands. The ducts are lined by cells resembling those of the basal-cell layer, and the lumina contain a hyalinelike material.

Destruction of these little tumors by the electric cautery gives satisfactory cosmetic results.

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Pigmented Nevus and Melanoma

By

S William Becker

Melanin pigmentation in man. In contrast with the highly colored coats of some lower animals and the gaudily plumed birds, man is a rather drab creature. It has not been generally appreciated that human beings carry in their skins a syncytium of potentially pigment forming cells which play a role in physiologic pigmentary processes such as occur in pregnancy and tanning and contribute by benign and malignant neoplasia, respectively to the two most important pigmented tumors namely pigmented nevus and melanoma.

The stem cells of these tumors are called melanoblasts and the mature pigment forming cells, melanocytes Skin apparently lacking in pigment, as in complete or partial albinism and vitiligo, contains the same sheet of cells, although they have been involved in depigmented abnormalities because of lack of tyrosinase. Nonpigmented nevus and melanoma may occur in such areas. The pigmented cells of this sheet also participate in supplying melanin to other tumors namely seborrheic keratosis and pigmented epidermal carcinoma. Many of the misunderstandings relative to abnormal pigmentary processes and tumors result from a lack of knowledge of normal pigmentation.

The single-layered syncytium of special cells is located at the junction of the epidermis and dermis. Because branches from these cells extend into the epidermis, they are inclined to be more closely attached to this layer in procedures that separate the epidermis from the dermis for study The syncytial arrangement of melanocytes at the epidermal-dermal junction had been mentioned by several authors, including myself on the basis

of isolated observations, but it remained for Becker Jr., and his associates and others to demonstrate the sheet convincingly and to further our knowledge of it. The disputed Langerhans cell is an integral part of this sheet.

The origin and nature of human melanocytes has been uncertain. However it was first demonstrated in amphibians then in fowl, and in mammals as high as mice that the cells originate from the neural crest and migrate from there to the epidermis. The cells differ from palisade basal cells in all respects They take stains which are useful in staining nervous tissue, such as methylene blue, and silver and gold salts In addition, they are the only cutaneous cells which contain tyrosinase and dopa-oxidase, as demonstrated by the tyrosine and dopa reactions.

Melanocytes are most easily seen in epidermis which has been separated from dermis in the form of regularly distributed, dendritic cells with oval or irregular bodies lying parallel to the cutaneous surface. The dendrites of one cell connect with those of adjacent cells, thus forming the syncytium. In ordinary cutaneous sections, the bodies are located at the epidermal-dermal junction, either in the basal layer between the palisade basal cells or between the basal cells and the papillae and superficial dermis. The branches may or may not be visible.

Pigmented nevi are formed by benign neoplasia of melanocytes. They are more common in Caucasians than in other races and show no sex difference. There is a definite hereditary disposition, especially to the larger lesions The extensive nevus is often accompanied by increase in meningeal melanocytes in the pia mater about the medulla and elsewhere in the central nervous system.

Lentigo profusa is the term used to signify extensive distribution of macular or maculopapular nevi. In some instances they are localized and unilateral, but they may be generalized, as in the case reported by Zeisler and me. Nevi are darkened by hormones in puberty and pregnancy and by ACTH and the melanin-stimulating hormone of the pituitary gland. They follow a rather predictable course. The macular nevi of childhood may remain as such, but usually they become maculopapular or large enough to be designated tumors sometimes lobulated, and with

an appearance of fissuring. The larger ones may become hairy usually at puberty but occasionally before. In a small percentage of cases, malignant melanoma may develop in a nevus but most nevi remain benign throughout life.

Acquired nevi appear at varying periods of life, from puberty onward. At first they are flesh-colored and often multiple, becoming pigmented later and usually remaining benign.

Some authorities believe that all nevus cells develop from melanocytes at the epidermal-dermal junction, while others believe that they may also develop from nervous elements possibly from schwannian cells in the dermis The schwannian origin is more strongly suggested by the peculiar nevi which have been called "prepubertal melanoma" by Pack, "juvenile melanoma" by Spitz, and for which I prefer the designation "juvenile pseudomelanoma."

Juvenile pseudomelanoma is a solitary nonpigmented or slightly pigmented lesion, occurring before puberty and occasionally after which has limited growth, does not metastasize, and is cured by complete local excision

The question of biopsy of a nevus is still in dispute. I have been removing nevi in part or in toto for biopsy for about 30 years and have never seen malignancy develop from such a procedure. The only sure method of diagnosis is by biopsy although I have never found malignant change in a lesion which, on clinical and anamnestic considerations, was a quiescent nevus.

The cells of nevi are not very anaplastic and are rarely cast off with the stratum corneum. Round cell infiltrate is minimal or absent.

Juvenile pseudomelanoma differs from nevi by the presence of a large number of nonpigmented fusiform cells some multinucleated giant cells, fewer oval and round pigmented cells, superficial telangiectasis and slight lymphocytic infiltrate. As in ordinary nevi, pigmentation is limited to the superficial cells.

Blue nevus. Appearing at any time during life a bluish macule or maculopapule may appear on any part of the body The color is provided by melanin contained in fusiform melanocytes in the dermis the blue hue usually being explained as caused by the scattering effect of the tissues overlying the pigment. Blue nevi

usually remain small but occasionally enlarge to cover a considerable area. They rarely become malignant to form melanoma.

In some instances there is admixture of nevus and blue nevus, in which case fusiform cells characteristic of blue nevus are seen in varying numbers, in part or throughout the nevus. The chief implication of the combination is the danger of diagnosing the lesion as melanoma.

Junction nevus. This term has been used frequently in the past few years and has led to some confusion. *All nevi are junctional* at first, because the melanocytes are in that region. In childhood they may be quite active and produce considerable epidermal hyperpigmentation. Since lentigo maligna also arises at the junction of the epidermis and the dermis not as benign but as malignant neoplasia, this lesion has also been called a junction nevus. Hence, when the designation junction nevus" is seen, it is necessary to determine whether a quiescent nevus, active nevus, or lentigo maligna is meant, in order to evaluate the statement. The designation should probably be abandoned.

Microscopic Classification of Pigmented Nevi. I suggest the following microscopic classification of pigmented nevi.

Type A Lesions in which nevus cells are still definitely attached to or actually integrated into the epidermis.

Type B Lesions in which no nevus cells are definitely attached to the epidermis, but in which they are present in the dermis.

Type C Nerve nevus type of Masson, some portions of which resemble neurofibroma.

In my series of 741 nevi, microscopic classification was

Type of Nevus	*Number of Cases*	*Percentage*
A	16	2.1
A and B	65	8.7
B	122	16.4
B and C	477	64.6
A, B and C	49	6.6
C	12.	1.6
Total	741	99.7

DIAGNOSIS

Knowledge of the life history of both nevus and melanoma is of paramount importance in diagnosis. If a careful clinical evaluation is combined with a careful history diagnosis of pig

mented nevus should not be difficult. A dark brown lesion which has persisted since childhood and has not shown pronounced increase in size or darkening is usually a pigmented nevus. The earliest tabulation of the diagnosis of pigmented nevus was made by me (Tables 1 and 2)

TABLE 1

LABORATORY DIAGNOSIS OF 710 LESIONS DIAGNOSED CLINICALLY AS NEVI

Diagnosis	*No. of Cases*
Nevus	587 (80%)
Seborrheic keratosis	39
Papilloepithelioma	20
Carcinoma	17
Verruca vulgaris	10
Chronic inflammatory lesion	7
Fibroma molle	6
Lentigo maligna	5
Fibroma	3
Neurofibroma	3
Lentigo	3
Melanoma	3
Adenoma sebaceum	2
Senile elastosis	2
Fibroxanthoma	2
Melanosis	3
Lentigo maligna with melanoma	1
Condyloma acuminatum	1
Xanthoma	1
Nevus sebaceus	1
Angiofibroma	1
Pseudoxanthoma elasticum	1
Hemangioma with hemorrhage and thrombosis	1
Duct of mucous gland	1
Sarcoid	1
Keratosis senilis	1
Lymphangioma	1
Leukemid	1
No diagnosis made	9

TREATMENT

Pigmented nevi are treated for cosmetic reasons or as prophylaxis against the formation of melanoma. Those treated for cosmetic reasons are more apt to be on exposed surfaces, while those removed prophylactically are at points of friction or pressure Large nevi of several centimeters in diameter are treated even if on covered surfaces.

The belief that partial destruction of a nevus is dangerous because of the induction of melanoma has given way to the realiza-

TABLE 2

CLINICAL DIAGNOSES OF 649 LESIONS DIAGNOSED MICROSCOPICALLY AS NEVI

Diagnosis	*No of Cases*
Nevus	567 (67%)
Seborrheic keratosis	15
Carcinoma	14
Fibroma molle	9
Verruca vulgaris	7
Lentigo maligna	6
Papilloepithelioma	6
Adenoma sebaceum	5
Cyst	5
Fibroma	4
Melanoma	3
[illegible]	1
[illegible]	1
[illegible]	1
[illegible]	1
Epithelioma adenoides cysticum	1
Granuloma pyogenicum	1
Actinodermatitis	1
Fibroangioma (mouth)	1

tion that such lesions are already malignant before treatment. There is no authentic report in the literature of malignant degeneration from treatment of a pigmented nevus. I have treated many thousands of pigmented nevi, usually by partial destruction under local anesthesia and have never seen malignant change in such an area.

There are, however certain cautions that must be exercised. The lesion to be treated should be quiescent, in other words, should not be growing or becoming darker The surface of the lesion, including the epidermal-dermal junction with its melanocytes, must be removed or destroyed, since it is only in this region and from this source that melanoma develops in a nevus.

The various methods of treatment of a pigmented nevus are: removal of the lesion in its entirety or the superficial portion, or destruction of the superficial portion. The former method has the advantage of preserving the superficial portion for biopsy which I believe is the only absolute method of eliminating melanoma as a possibility

My own treatment of pigmented nevi is as follows:

Macular nevus. Most small macular nevi which are treated are on the face. If there is no history of tendency to enlarge or

become darker destruction of the epidermal-dermal junction by the electric cautery or fulguration suffices to produce an acceptable scar A brown lesion on the face which is growing should be biopsied to rule out lentigo maligna. Large macular nevi are treated by plastic surgery

Papular nevus. If there is no history of darkening and rapid growth, the *superficial portion is snipped off* with *scissors* and the remainder is treated with the electric cautery deeply enough to insure a smooth scar The removed portion is sent to the laboratory for biopsy Larger elevated nevi may be removed by plastic surgery

Hairy nevus. The papular hairy nevus may be treated in one of two ways as a papular nevus, with subsequent removal of returning hairs by the epilating needle, or after preliminary epilation, biopsy specimen may be removed and the lesion cauterized at the same visit.

Extensive nevi. Often hairy especially after puberty they are removed by the plastic surgeon, usually in parts. Because of the stimulating effect of estrogens it may be advisable to remove them before puberty although several instances of the development of malignancy before puberty have been reported.

Blue nevus. The only satisfactory treatment for blue nevus is surgical excision.

MELANOMA

Malignant melanoma is probably the most dangerous and malignant tumor that afflicts mankind. Its potential danger lies in its insidious course the slowness of which belies the statement of its great malignancy Mortality even with the best of treatment, runs at present about 70 per cent, which is much too high for a tumor that is almost always visible and usually curable if recognized early and treated adequately

If we examine the literature we will find that it is stated that:

1 Most melanomas arise from pre-existing nevi. Actually however evidence of a pre-existing nevus either from history or in microscopic sections, can be obtained in not over 25 per cent of instances. Some of the confusion has arisen from the erroneous use of the term junction nevus for lentigo maligna which is not a nevus but rather a melanoma in situ. The sites of the appearance of melanoma do not correspond to those of pigmented nevi,

as shown by Pack. However as I have emphasized, if one estimates the body surface as 16 000 sq cm., and the surface of the 10 to 80 nevi possessed by the average person as much less than 100 sq cm., melanoma occurs relatively more frequently in nevi than in normal skin. Many nevi show more prominent melanocytes in the epidermis than in the adjacent normal skin.

2. The influence of trauma to nevi is of importance in the causation of melanoma. The reported instances of trauma usually occurred after and not before malignancy had supervened. This does not mean, however that repeated trauma cannot initiate melanoma formation in some instances.

3. Contact x-ray therapy for melanoma is as efficient as surgical excision. This statement does not seem to consider the penchant of melanoma to spread widely in the deep lymphatics, which can be reached only by some form of surgical removal.

4. Melanoma metastasizes early often by the blood stream. Blood stream metastasis takes place, possibly not early in a small percentage of cases and of course can not be combated once it has taken place. However the usual spread via the lymphatics, which occurs some months or years after the appearance of the early primary lesion, should be considered the normal course and combated by radical surgical procedures.

5. Melanoma is rare before puberty and is not apt to metastasize at that period of life. There is no doubt that melanoma is rare before puberty which is attested to by the fact that from 1838 to the present time there are only 84 reports of cases of melanoma in infancy and childhood, of which 13 had recurrence after treatment, 42 had metastases, and 23 were reported to have died from the disease. Nevertheless, one should observe all precautions when there is a picture of true melanoma in a child. The occurrence of juvenile pseudomelanoma before puberty with its relative or absolute benignity has given a false sense of security in dealing with a real melanoma in childhood.

The individual who is most apt to develop melanoma is the light complexioned person who sunburns easily Patients with xeroderma pigmentosum are also more apt to develop melanoma than other persons. Here, though, it is usually females who are afflicted and at an earlier age than other individuals. Their

melanomas are apt to be of the spindle-cell variety which tend to be less malignant clinically than the round and oval-cell types

From figures compiled in the state of Connecticut, 2300 new melanoma patients should consult physicians each year in the United States. At the University of Chicago Dermatological Laboratory the ratio of cutaneous carcinoma to melanoma is 37 1 Melanoma is equally divided between the two sexes. However the hormonal changes during puberty and especially pregnancy have a definite stimulating influence on melanoma production and the rapidity of spread.

Let us examine the life history of melanoma. Melanoma arises as malignant neoplasia of melanocytes at the epidermal-dermal junction. In most instances, a dark brown lesion appears in normal skin, known as lentigo maligna. If accurate history is taken, it will be found that lentigo maligna has been present for months and even years before metastasis takes place. Once the tumor stage is evident, metastasis may be expected. This has probably been responsible for the statement that melanoma spreads early with the incidence dated from the tumor stage. Since the tumor stage appears only after months and even years, this development may be regarded as late rather than early

Everyone agrees that the tumor constitutes real melanoma. It may be red and resemble pyogenic granuloma, but it may also be brown or black. In the cases of melanoma arising in a nevus, the tumor stage may be the first one that is noted, since the change from a benign nevus to melanoma is a gradual one.

The spread of melanoma is both superficial and deep. The superficial extension may appear in the form of satellite lesions near the primary tumor often black in color and close to the primary tumor In the meantime, however the spread in the deep lymphatics is much wider eventually to the regional lymph nodes which at first are not greatly enlarged. The tumor later extends to the lymph nodes next in line and eventually into the blood stream, either directly from the lymph nodes or via the thoracic duct. It colonizes in all tissues of the body in contrast with most other tumors In generalized melanoma, the urine may become dark, either as it is passed or on standing In rare instances the

tissues of the entire body become dark and even black, because of appearance of melanin throughout the entire body

Ten per cent of melanomas are *first recognized as metastatic* growths in regional lymph nodes, after which the primary may or may not be found. At times, a history will be obtained of previous removal of a tumor in the region draining into the nodes. In large series of patients, failure to find the primary tumor obtains in 10 to 15 per cent of cases. In rare instances, the primary tumor may rise above the clinical threshold only years after the appearance of nodal metastasis.

Since the melanocyte sheet extends onto the mucotaneous junctions and mucosae, melanoma occurs in these regions, although less commonly than on the skin. Diagnosis is more difficult here than on the skin, as 50 per cent of such tumors are nonpigmented.

DIAGNOSIS

All writers indicate that the clinical diagnosis of melanoma is difficult, hence it cannot be relied upon The concept so frequent in the literature that melanoma should not be biopsied is now changing because of realization that biopsy seals the lymphatics for a time and temporarily deters spread. However the physician should be prepared to carry out adequate treatment as soon as the diagnosis is verified.

I previously reported statistics showing that only 43 per cent of 169 clinically diagnosed melanomas proved to be so microscopically (Table 3) and that only 48 per cent of microscopically proved melanomas had been diagnosed clinically (Table 4) There was an unduly large number of clinical diagnoses of pigmented nevi, which suggests that there is a tendency to such a diagnosis on brown lesions without careful clinical and anamnestic considerations, thus closing the mind to the possibility of melanoma. Much difficulty has been experienced in microscopic diagnosis of melanoma, because of its tendency to simulate other tumors: carcinoma (fusiform and other varieties) fibrosarcoma, lymphosarcoma, liposarcoma, endothelioma, perithelioma, and Wagner Meissner corpuscles. The cells are more anaplastic, are often cast off with the stratum corneum, and pronounced lymphocytic infiltrate is present in early lesions. The dopa reaction is

TABLE 3

LABORATORY DIAGNOSIS IN 169 CASES DIAGNOSED AS MELANOMA CLINICALLY

Melanoma	72 (43%)
Nevus pigmentosus	18
Blue nevus	14
Melanotic carcinoma	10
Lentigo	10
Seborrheic keratosis	7
Thrombosed angioma	5
Verruca vulgaris	5
Angiofibroma with hemorrhage	3
Metastatic melanoma, squamous-cell carcinoma, senile keratosis, tattoo, dermatitis, nevus, and blue nevus	2 each
Bowen's disease, mixed tumor of parotid gland, blood cyst with thrombosis, neurofibroma with hemorrhage, acquired nevus pigmentosus, Kaposi's sarcoma, carcinoma with hemorrhage, lupus vulgaris, chronic inflammation with melanosis, adenoma sebaceum, mucous cyst, granuloma pyogenicum, nonspecific ulcer	1 each

TABLE 4

CLINICAL DIAGNOSIS IN 151 CASES OF MELANOMA VERIFIED MICROSCOPICALLY

Melanoma	72 (48%)
Nevus pigmentosus	36
Seborrheic keratosis	7
Granuloma pyogenicum	7
Carcinoma	5
Melanotic carcinoma	4
Lentigo	4
Fibroma	3
Thrombosed angioma	2
Sebaceous cyst	2
Angiokeratoma, angiofibroma with hemorrhage, mixed tumor of parotid gland, blue nevus, Kaposi sarcoma, sarcoid, tumor, leukoderma acquisitum centrifugum, melanosis	1 each

apt to be positive, and Fitzpatrick and Lerner showed that even nonpigmented melanoma gives a pronounced tyrosine reaction, which should prove to be of great value in differentiation of questionable nonpigmented neoplasms.

TREATMENT

Treatment of melanoma consists of removal or destruction. Knowledge of the life history is a partial guide as to where the tumor may be expected to have extended at any given time. If the patient seeks medical care early the surgeon has ample time to institute radical therapy From the time of onset of lentigo

maligna, several months and usually years pe[illegible]
plasm reaches the regional lymph nodes. [illegible]
ing slowly in both the deep and superficial [illegible]
widely in the deep. Considerable judgment [illegible]
choosing a sufficiently extensive operative [illegible]
mum operation consists of removal of a wide [illegible]
with superficial and deep fascias, since the [illegible]
course in the latter It seems to me that [illegible]
have resulted from a too limited removal of [illegible]
tumor area.

It is difficult to determine just when the [illegible]
should be removed. Many workers have [illegible]
nodes in which metastatic melanoma has [illegible]
clinically enlarged in at least 50 per cent [illegible]
palpable enlargement can not be safely used [illegible]
removal. Of course, the longer the process [illegible]
the greater the possibility of metastasis to [illegible]
nodes. I have seen lentigo maligna of the [illegible]
duration with no palpably enlarged femoral [illegible]
nodes. However after local removal of the [illegible]
appeared later in the inguinal lymph nodes, [illegible]
cumbed to the disease. It therefore seems [illegible]
the process has not advanced beyond the [illegible]
removal of the regional lymph nodes is indi[illegible]

It is my impression that node removal [illegible]
enough to insure the best possible resu[illegible]
lymph nodes is not a serious procedure, it [illegible]
it is better to err on the safe side and [illegible]
regional lymph nodes whenever a definite [illegible]
the skin. This procedure permits micr[illegible]
the nodes for possible metastasis. A can[illegible]
to remove the lymph nodes than is a ger[illegible]

In instances where melanoma has arise[illegible]
extra care should be taken to remove th[illegible]
because it is impossible to estimate the o[illegible]
a tumor has always been present in the [illegible]

Contact roentgen therapy which is [illegible]
European clinics can only be successful [illegible]

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Treatment of melanoma consists of removal or destruction. Knowledge of the life history is a partial guide as to where the tumor may be expected to have extended at any given time. If the patient seeks medical care early the surgeon has ample time to institute radical therapy From the time of onset of lentigo

9 Subsequent observation is important, because recurrent lesions should be removed immediately on discovery if accessible.

10 The actual five year survival rate varies with different authors. Pack, who has observed the largest group, reported 28.2 per cent of five year survivals.

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33

Familial Benign Chronic Pemphigus

By
Howard Hailey

FAMILIAL benign chronic pemphigus which I first observed in two brothers in 1936, is now considered and accepted as a definite entity I saw the disease in one of two additional male patients of Dr J Richard Allison of Columbia, South Carolina. With Dr Allison s permission I reported his two patients along with mine in 1939 Since this first report, I have seen in more than 20 families one or more members affected by familial benign chronic pemphigus. My most recently published report on this subject was read at the meeting of the Tenth International Congress of Dermatology held in London in 1952. Two patients, a brother and sister with the disorder were presented at the clinic conducted for the attending dermatologists. The father of these patients had had the disease all of his life- he died at the age of 75.

In all, I have seen over 100 persons with the disorder all of whom were of the whi ... I have not en ... ered the disease in Jews. Two c ... lleagues residin ... other States have each seen one ... familial ben ... nic pemphigus.

The name, familial b ... c pemphi ... selected because of the ... rac ... escript ... isease. The disease ... t lon ... t disturbed, the ... ti- tutional sym ... ated by re ... lesions arise ...

The disord ... twenties the ...

age and the oldest 88. As the patient grows older the attacks usually become more infrequent and less severe.

The primary lesion is a vesicle or bulla arising on apparently normal skin. Nikolsky's sign is present, it is demonstrated by applying pressure gently and firmly over a bulla, which causes the serum to advance and separate the layers of epidermis. These lesions rupture early leaving a moist erosion, the serum drying to form amber-colored crusts creating an impetigolike picture. The lesions vary in size and are always sharply demarcated. The pellicle at the edge of the lesion may often be picked up with forceps and peeled back, if done carefully The lesions usually heal in a week or so, leaving areas of erythema marking the pattern of the lesions. In due course of time, temporary hyperpigmentation follows. Subsequent atrophy or scarring never occurs.

Although any part of the body may be affected, the sites of predilection in descending order of frequency are the collar region, axillae, and groin. Even the skin about the eyes and anus participates at times in the disease. In two patients recently observed, there was involvement of the hands and arms in addition to that of the neck and axillary regions.

Although not a constant feature of the disease, the regional lymph nodes may be enlarged. Due to heat and perspiration, the disease is worse in warm weather Pruritus is a constant feature but varies greatly in severity and seems to be influenced by the size and location of the lesion, the neglect of the serous discharge the stability of the patient's nervous system, and by his occupation.

The diagnosis of familial benign chronic pemphigus is easily made on the clinical appearance of the primary lesion which consists of a vesicle or bulla which soon ruptures and usually becomes confluent with an adjacent lesion to form an area from which serum flows and dries to form an amber-colored crust. The exfoliation of the dry scales completes the resolution of the lesion, leaving areas of erythema followed in due course by pigmentation of a temporary character The histologic examination of biopsy specimens is rarely necessary to establish the diagnosis, the clinical picture being so highly characteristic.

The history and course of the disease make it fairly easy to differentiate it from epidermolysis bullosa, erythema multiforme, dermatitis herpetiformis, drug eruptions, and true pemphigus. *In my opinion, Darier's disease should never be considered seriously in the differential diagnosis*

I have never seen a patient with familial benign chronic pemphigus in whom the clinical diagnosis was not substantiated by the histologic examination of properly selected biopsy material.

The two most prominent histologic features are intradermal vesicles and bullae and a single layer of basal cells attached to the dermis *The suprabasal separation of the epidermis, due to* edema, produces irregular spaces or fissures which suggest the picture of a dried-out mud bank. Acanthosis is a constant feature, but hyperkeratosis is not always present. Cellular exudation is present in the lacunae or bullae. The prickle cells are edematous, and there is lymphocytic infiltration in the dermis.

The etiology of the disorder is not known. The geneologic chart which I prepared for an earlier article on this subject shows four generations in which nine males and four females were affected with familial benign chronic pemphigus. Of these 13 persons, I observed five all five presenting the same clinical picture

There is no specific treatment. Recently I had several patients who recovered from acute attacks more quickly than usual following the use of one of the triple-sulfonamides in conjunction with the local use of 2 per cent boric acid wet dressings until the oozing stopped. Each 0.5 gm sulfonamide tablet consists of equal parts of sulfadiazine sulfamerazine and sulfamethazine· one tablet is given every four hours during the waking period.

The use of one per cent hydrocortisone acetate ointment shortens the duration of attacks in patients who are in the early dry stage of the disease· it should be applied sparingly three times daily I believe that x ray therapy over the affected areas at intervals of four to seven days is beneficial, the dosage being *45 r to 75 r of* unfiltered radiation at each session.

In my experience the antibiotics are of no value internally or locally in shortening the duration of the disease. Vitamins are also ineffective. Patients are inclined to give credit to any prepa-

ration which they are taking or using locally at the time of recovery from an acute attack, and I urge the attending physician to avoid the use of strong chemicals, various types of adhesive tape, and ultraviolet light in the management of this disorder because of the probability of rapid and widespread extension of the process.

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34

Scleroderma-Dermatomyositis

By
Julio M. Borda

THIS CONTRIBUTION is based on my experience of 20 years with *40 patients with generalized scleroderma, three with scleredema* adultorum, 24 with dermatomyositis and 33 with circumscribed scleroderma, including several varieties of lichen sclerosus et atrophicus and related disorders.

It is my belief that these disorders are closely interrelated and that they may be classified as follows

- Scleroderma
  - Generalized
    - Acrosclerosis
    - Scleredema adultorum
    - Sclerema of the newborn
  - Circumscribed
    - Patches
      - Common type
      - Regional systematized type
      - Lichen sclerosus et atrophicus
    - Band type
    - Ainhum ?
- Dermatomyositis
  - Classic dermatomyositis
  - Complicated by the development of
    - Poikiloderma
    - Poikilodermatomyositis
    - Calcinosis universalis

GENERALIZED SCLERODERMA

Acrosclerosis represents the commonest form of generalized scleroderma. Like most other forms of scleroderma, other organs in addition to the skin participate in the general disorder and become the seat of sclerotic changes. It is therefore a systemic disease which I believe begins in the blood vessels, involving secondarily the connective tissue of the skin muscles, and viscera. Although the hands are commonly believed to be the most severely affected areas, severe involvement of the viscera and striated musculature invariably occurs coincidently

without becoming evident until sclerotic changes interfere with the function of the affected viscera or muscle. Occasionally however there are signs of visceral involvement previous to the appearance of cutaneous lesions.

The earliest visible symptoms of generalized scleroderma are most commonly those of Raynaud's disease with repeated episodes of arteriolar spasm induced particularly by cold. It is my experience that symptoms of Raynaud's disease are indicative of incipient generalized scleroderma until proved otherwise, as for instance in the case of thromboangiitis obliterans, arteriosclerosis, or scalenus anticus muscle syndrome.

The initial symmetrical involvement of the tips of the fingers gradually spreads up over the knuckles, hands, and the forearms to lose itself in the skin about the elbow The development of painful run arounds of the terminal phalanges which culminate in the discharge of pus and scarring is not the result of an underlying trophoneurosis but rather of vascular obliteration and subsequent inflammatory changes in the affected areas.

The frequent formation of painful verrucous growth on the ball of the fingers suggests that we are dealing with obliterative changes in the walls of the collateral blood vessels, since I have seen similar lesions in a patient with endarteritis obliterans

With the gradual development of bullae, keratoses calcified nodules, nail dystrophies, and mutilations, the patient is brought to a sorry pass, not being able to use his fingers.

Contrary to general belief, neither the skin of the legs nor of the face participates in the disorder The skin of the face becomes stretched and taut, losing the lines of expression because of sclerotic involvement of the muscles of expression, not because of sclerotic changes in the skin

Sclerotic involvement of the skin of the neck and upper part of the chest almost always takes place in advanced cases, the affected regions resembling areas of poikiloderma. Involvement of the entire cutaneous surface is exceptional.

Hyperpigmentation may be superimposed on the involved areas, together with patches of vitiligo.

I believe that the occurrence of painful torpid abscesses in patients with generalized scleroderma is of great etiologic signifi-

cance Furthermore, as an indication of the vascular component in the pathogenesis of the disorder the frequent appearance of lesions which causally are not directly related to vasospasm is worthy of mention. These lesions include angiomas, telangiectases, ulcers resembling chronic leg ulcers in areas other than about the knuckles and ankles, and lesions of gangrene and purpura.

Symptoms suggesting the part played by hypersensitivity in the pathogenesis have not been sufficiently emphasized in the literature. Several patients included in this series have shown urticarial or prurigolike lesions associated with intense itching. One subject had a severe attack of urticaria preceding the appearance of sclerosis. Another showed widespread lichenification with itching These allergic manifestations could not be imputed to a coincidental universal itching eruption due to scabietic infestation, as occurred in a patient with scleroderma reported by Turner and Schmidt and in one of my patients as well.

In considering the constitutional symptoms, I shall limit myself to a discussion of those which I consider of importance from an etiologic standpoint, those showing a relationship to symptoms encountered in related sclerotic disorders, and those in dermatomyositis and its sequelae.

An almost constant feature in most patients is the involvement of the striated musculature, occasionally occurring as the first indication of the disease Two patients in this series had had several attacks of acute myositis before frank symptoms of scleroderma appeared Other symptoms of participation of the muscles in the general disorder are weakness difficulties in swallowing and speaking, and loss of the lines of expression.

The hemocytologic changes encountered in these patients are such as to suggest an infectious origin of scleroderma. The triad of anemia, increased erythrocyte sedimentation rate and leukocytosis occurred in almost all patients A red cell count of around 3,500 000 was the usual finding, and a relative and absolute increase in the number of polymorphonuclear leukocytes was usually encountered. One patient showed an increase in the number of eosinophils averaging 25 per cent. The erythrocyte sedimentation rate varied between 30 and 40 U W (Katz)

The blood count and sedimentation rate became normal whenever it was possible to eliminate the focus of infection.

Symptoms referable to the gastrointestinal tract are constant features of most cases. One symptom is especially worthy of mention, consisting of regurgitations associated with intense pain occurring from one to two hours after the patient goes to bed. This is, I believe, a symptom of cardiac insufficiency

In one patient there was a tumor of the parotid gland. Histologic sections of the tumor showed sclerotic obliteration of the acini. The resultant clinical picture is similar to that seen in Sjögren's syndrome with dryness of the mouth and eyes. The liver ultimately becomes cirrhotic or shows calcareous deposits in the capsule.

Psychic disturbances are a feature of most cases. It is probable that they are brought on by nervous or emotional stresses resulting mainly from economic worries, since scleroderma rarely occurs in people of means. Patients with this disorder usually develop into hypochondriacs as a result of these psychic disturbances.

There are many other psychic disturbances in these patients, resulting from what I believe are anoxic episodes of the higher cortical centers induced by spasm of the cerebral blood vessels occurring in the initial phases and exacerbations of the disorder One woman had extreme loss of memory associated with frequent changes of personality simulating psychic disturbances in epileptics. Another patient became completely demented and had to be placed in an institution. One patient became demented with symptoms of extreme depression and hypochondria a few days before dying of cardiac decompensation induced by large doses of nicotinamide.

The almost constant occurrence of symptoms of endocrine disturbance in patients having scleroderma has led to the belief that the disorder is caused by initial sclerotic changes of the endocrine glands. I believe, however that the sclerotic changes encountered in the endocrine glands are merely solitary manifestations of anoxia and thrombosis occurring simultaneously throughout the body Because of the vascular structure, the thyroid gland, ovaries, and other endocrine glands are among the first to suffer

from interference with the blood supply resulting in such clinical pictures as Simmond's cachexia hypophysea.

Etiology and pathogenesis. The observations cited in the fore going pages have convinced me of the primacy of vascular in volvement in the production of scleroderma. I refer particularly to arteriolar spasm and obliterative changes in the blood vessel walls occurring in the initial phases of the disorder

Vascular changes in scleroderma were recognized by Mery as early as 1889 Many of the common symptoms are provoked by these vascular changes, including Raynaud's phenomenon, telangiectases chronic leg ulcers purpura, and myocardial infarcts.

In further support of this concept is the observation of a patient who had several attacks of intermittent claudication, which in the course of time were followed by symptoms of myocardial infarction and ultimately by the appearance of scleroderma in band form on the chest. In this connection, it will be recalled that Buerger regarded scleroderma as a vascular disease citing a case of scleroderma associated with thromboangiitis obliterans in support of his contention.

What then is the precipitating factor in the production of vasospasm? Two sets of experiments are of prime importance in establishing this factor The first of these studies, carried out by Sanarelli, demonstrated that subtoxic doses of bacterial filtrates injected intravenously in rabbits at 24-hour intervals invariably provoked a succession of severe and widespread hemorrhages associated with thrombosis of the veins of the liver spleen, pancreas and lungs In addition, there were fibrinoid degeneration and necrosis of the renal glomeruli and of focal areas of the spleen, liver and heart.

In the second groups of experiments, Hitchcock, Camero and Swift showed that repeated sensitizing doses of streptococci injected intradermally in rabbits produced vasculitis, particularly of the vessels of the lungs and liver whenever a similar sensitizing dose of streptococcal antigen was injected intravenously

Similar findings were observed by Boughton in guinea pigs following the injection of sensitizing doses of egg white No one could ask for greater resemblance between the vascular lesions

induced in animals by bacterial and foreign protein and those representing the primary reaction of scleroderma.

In passing, it should be noted that these experiments were not initiated with the intent of demonstrating the mechanism of production of scleroderma but were merely additional experiments along the lines of Klinge and his coworkers in their studies of what they believed to be disorders caused by hypersensitivity

A review of the pertinent literature reveals abundant clinical evidence in support of the thesis that scleroderma represents a reaction to infection. Gate reported the case of a young man who had been vaccinated against typhoid and paratyphoid fevers on entering the army Following each of two successive annual "booster vaccinations, edema of the hands and forearms occurred. After the third revaccination, the edema became widespread, and generalized scleroderma developed.

A patient of Thibierge, Spillmann, and Weissenbach developed scleroderma associated with calcareous deposits, following an injection of diphtheria antitoxin.

A patient of mine had had repeated attacks of boils and other pyogenic infections throughout most of his life and became highly sensitized through repeated therapeutic vaccinations against these infections. Upon the advice of a physician, a dentist extracted all of his teeth at the rate of four every three days. After each session he had an episode of headache, weakness, and fever One month after the termination of these wholesale extractions symptoms of generalized scleroderma appeared.

The course of events in this man may be attributed to the mobilization of bacterial agents lodging in the peridental spaces and the entrance of the agents into the blood stream acting as an intravenous injection of antigen in a previously sensitized subject. In further support of the allergenic nature of scleroderma, I would like to add that the patient showed marked improvement following a series of desensitizing injections of staphylococcal-streptococcal vaccine.

The concept of hypersensitivity as constituting at least one of the causes of scleroderma allows us to broaden our concept of the etiology and pathogenesis of the disease. The situation

is analogous to that in asthma, in which any one of several agents may precipitate an attack.

Furthermore, it is my experience that the disorder is frequently associated with such manifestations of hypersensitivity as itching, urticaria, and papular urticaria.

Treatment. Symptomatic treatment of this disease has been a failure in my experience This applies with few reservations to the use of hormones of the endocrine and adrenal glands, vitamins, and other preparations. The administration of corticotropin or the cortisones may however be useful in the early phase of the disorder Their use is also distinctly serviceable during depressive episodes, due to their tendency to bring on euphoria.

The treatment of choice, in my opinion, is elimination of the focus of infection in the individual case. A few examples from my practice will serve to emphasize this dictum.

A woman aged 28 showed notable improvement with apparent arrest of the disease following tonsillectomy and treatment for intestinal amebiasis The pains in the ankle and the cramps and numbness of the legs disappeared. The "run arounds" became less in number and severity She has not only regained the weight that she had before her illness but some 29 pounds more than she ever had in her life

A woman having associated psychic and joint disturbances of great severity responded favorably to treatment of an underlying syphilitic infection with bismuth.

Another patient with coexistent symptoms of adrenal insufficiency consisting of hypotension asthenia, generalized dusky pigmentation of the skin and difficult swallowing, showed great improvement following tonsillectomy and extraction of infected teeth. Recovery was hastened by the administration of adrenocortical extract and by esophageal dilation

A woman with coexistent prurigolike lesions received considerable benefit from tonsillectomy and extraction of infected teeth. She failed to improve beyond a certain point, when one day she developed severe abdominal pains indicative of appendicitis. At operation extensive areas of peritonitis were found in the appendiceal region. After an uneventful recovery the sclerodermic process became inactive

The hemocytologic changes and the sedimentation rate of erythrocytes gradually returned to normal as the fever abated. The gradual disappearance of these symptoms, in conjunction with the weight curve, serves as a reliable index of the effectiveness of therapeutic remedies.

Scleredema adultorum is a form of scleroderma characterized by the occurrence at any time of life of widespread edema and induration of the skin following an infectious disease. The mobility of the affected parts is limited. Complete restitution of function and structure usually takes place in a few months.

I shall confine my discussion to certain clinical, etiologic, and evolutionary aspects which serve to emphasize the relationship between scleroderma and dermatomyositis and which support the concept of infectious origin and vascular pathogenesis of this group of disorders. However the situation regarding the onset of lesions differs in members of this group In scleredema adultorum, for instance, they appear following a previous infection, whereas in generalized scleroderma this is not usually the case.

The disorder most commonly follows an infectious disease such as influenza or tonsillitis. The skin is occasionally the site of the precipitating infection, as with erysipelas, bacterial dermatitis, and vaccination. In one patient the disorder arose following a peridental abscess and in another after an attack of parotitis. Another patient, at present under treatment for Raynaud's disease associated with incipient symptoms of generalized scleroderma, gave a clear-cut history of having had an attack of scleredema four years previously which had been brought on by pleurisy of undetermined origin.

These observations indicate that areas of skin adjacent to the antecedent infection are commonly the site of origin of the scleromatous process This is particularly evident in patients giving a history of peridental abscess or infection of the nose and mouth preceding the occurrence of scleredema.

Induration of the skin gradually supervenes, and the skin assumes the consistency of bacon or skin infiltrated with paraffin. Pitting on pressure does not occur Although the process commonly embraces several large areas of the skin, occasionally it involves the entire cutaneous surface. Participation of the mucous membranes has been reported.

Two patients showed large sclerotic areas symmetrically disposed over the trunk and extremities. One of these patients had a large sclerotic patch covering the entire back from the scapulae down to the sacrum, which closely paralleled the primary dorsal cutaneous segment.

Three other patients showed unilateral lesions of the legs and arms limited to the distribution of the primary mesenchymal layer

Lichen sclerosus et atrophicus is generally regarded as an independent disorder a concept to which I also adhered until recently The observation of several patients with coexistent morphea and lichen sclerosus et atrophicus and of others in whom typical lesions of the latter disorder became transformed into sclerodermic patches inclines me to believe that lichen sclerosus et atrophicus is merely a variant of circumscribed scleroderma occurring in patchy or guttate form

The *histopathologic studies* by Abulafia of material obtained from these patients confirm this concept (see p. 60) If we accept the identity of these two disorders the interpretation of conflicting opinions on this subject will be greatly facilitated.

With this in mind, I would like to suggest the following clinical types as variants of circumscribed scleroderma. These are forms which are currently regarded by many as variants of lichen sclerosus et atrophicus

1 Patchy lesions with such typical features as a yellowish color well-defined margins, and follicular dots. Dell formation is absent.

2. A type resembling poikiloderma, which is limited to intertriginous areas. At times, erosions occur particularly of the skin under the breast. This type is common in my experience

3. White spot disease which is characterized by nonelevated, white, soft lesions of variable size situated mainly on the upper chest and back, particularly in women.

4. Chronic atrophic lichenoid dermatitis which is a more generalized lichenoid eruption affecting the trunk and extremities.

5 Hemorrhagic lesions in the form of ecchymoses or petechiae

6. Bullous formation arising in the sclerotic patches

7 Involvement of the penis resulting in the clinical picture of balanitis xerotica obliterans.

8. Verrucous-covered lesions.

The majority of sclerotic lesions appearing in band form that I have seen are situated on the extremities and correspond to those of the regional systematized type previously described.

There is one type, however deserving of special mention. This consists of a sclerotic band involving the forehead and adjacent scalp in the midline, associated with areas of alopecia on the scalp Contrary to the experience of Rubin, I have only observed this condition as the sole manifestation of circumscribed scleroderma. The distinction of this type may sometimes be difficult from facial hemiatrophy an entity having a different clinical picture and evolutionary course

Ainhum is commonly regarded as a form of circumscribed scleroderma. Never having seen a case, my discussion will be limited to the authoritative opinion of Rabello. According to him, ainhum is a disease occurring only in Negroes and represents a congenital malformation manifesting itself in the genotype due to the action of environmental factors of which the most important one is injury This feature separates ainhum from mutilating forms of leprosy syringomyelia, and scleroderma. The distinctly different histologic picture of ainhum adds support to Rabello's contention.

DERMATOMYOSITIS

Dermatomyositis is characterized by vague prodromal symptoms followed by cutaneous lesions consisting of symmetrical areas of erythema and edema of the face, chest, and arms. The process is associated with fever of the intermittent type, progressive muscular weakness, and a characteristic histologic picture.

Synonyms expressive of involvement of the mucous membranes or the nerves are dermatomucomyositis or dermatoneuromyositis, respectively Another synonym is polymyositis. I shall limit my discussion to a brief summary of those symptoms which emphasize the close clinical, etiologic, and pathogenetic relationship of this disorder to scleroderma and related disease of the connective tissue.

The disease may occur at any age. Prodromal symptoms of a vague nature, lasting for days or weeks, or even longer are usually present, after which the typical lesions consisting of extensive

patches of edema and erythema make their appearance, predominantly on the face chest, and arms. The face is most markedly involved, the affected areas having a heliotrope tint and resembling acute actinic dermatitis. The edema, which is boardlike in consistency and does not pit on pressure, is limited to the areas of erythema. The knuckles and interphalangeal prominences also participate in the erythematous process.

Early congestive or bullous lesions of the mucous membranes are occasionally observed. In more advanced stages ulcers and patches of leukokeratosis may develop In one of my patients, exfoliative cheilitis and atrophy of the lingual papillae occurred.

The hair may become involved with the occurrence of hypertrichosis or alopecia areata. The sweat glands are commonly affected, resulting in hyperhidrosis.

The lesions in the muscles usually occur concomitantly with those of the skin. Occasionally however they occur previous to the appearance of cutaneous changes. In rare instances, they are the sole manifestation of the disease. The muscles of the thighs, arms abdomen and lumbar group are most generally affected, resulting in progressive weakness, muscular pain and ultimate atrophy of the muscles. Patients sooner or later complain of difficulty in dressing, brushing their hair swallowing, talking, and walking Impotence occurred in five of my patients. Involvement of the diaphragmatic or intercostal muscles is a serious complication

The edema gradually disappears in patients who survive, the redness fades out and atrophy supervenes. The lines of expression become effaced by the pull of the retracted skin, and the forehead appears dirty

The symptoms of atrophy which are characteristic of advanced stages of the disorder tally exactly with those of poikiloderma atrophicans vasculare. This similarity of clinical pictures suggests that poikiloderma atrophicans vasculare is a sequel of dermatomyositis.

Patients in the late stages of the disorder occasionally show calcareous deposits in the subcutaneous fat and viscera. At other times the calcification becomes generalized, coinciding with the condition known as calcinosis universalis. Langmead and Nor

regaard independently suggested that this form of calcinosis represents a late stage of dermatomyositis

Participation of most of the organs in dermatomyositis produces symptoms referable to the particular organ affected. These symptoms are universally well recognized and do not merit our consideration. Among the lesser known symptoms of systemic involvement are interstitial hemorrhages occurring in the hemorrhagic form of the disease. Death usually occurs as a consequence of myocardial involvement or of terminal pneumonia.

Histoanatomic studies of biopsies of the skin obtained from these patients are described by Abulafia (see p 58)

The blood shows increased numbers of leukocytes and eosinophils, eosinophilia being present in 50 per cent of cases. The sedimentation rate of erythrocytes is particularly high during exacerbations of the disease. An important laboratory feature is the increased urinary excretion of creatine and creatinine.

The distinction of dermatomyositis from subacute and acute lupus erythematosus is extremely difficult at times, particularly in the early stages. Demonstration of the L.E cells in the blood and of hematoxylin-staining bodies in the tissue is decisive. Trichinosis, myasthenia gravis, and the progressive muscular dystrophies must also be considered in the differential diagnosis.

Etiology and pathogenesis. The cause of dermatomyositis has not been definitely established. The observations cited in the foregoing pages lend weight to the concept that the disease represents a reaction of hypersensitivity to infection. Of the numerous infectious agents suggested as being responsible for the disease, the streptococcus and a dermatomyotropic virus are most frequently incriminated.

Coexistent carcinoma, particularly in women with involvement of the uterus, ovary and breast, is by no means rare. In a study of 336 cases, Schuermann found coexistent malignant growths in 7 44 per cent. Curtis and his collaborators found concomitant malignant disease in 17 7 per cent of their patients with dermatomyositis Two of my 13 patients had cancer

The multiplicity of alleged causative agents of dermatomyositis suggest that we are dealing with a situation similar to that in scleroderma, in which it is suggested that the sclerotic changes

represent a reaction of hypersensitivity to any one of several agents, particularly infection.

The management of the individual case should be guided by the establishment of the hypersensitivity factor The use of the adrenal steroids is effective in attenuating the tissue degeneration beginning to manifest itself in the early phases of the disorder In the final analysis the results of thorough clinical and laboratory studies should determine the type of therapy

SUMMARY

This report deals with the study of 76 patients with scleroderma and 24 with dermatomyositis. Those having scleroderma include 40 with generalized scleroderma, three with scleredema adultorum, and 33 with variants of circumscribed scleroderma such as lichen sclerosus et atrophicus, regional systematized types and those appearing in patchy lichenoid, or band form

Patients with dermatomyositis include those showing true dermatomyositis, poikiloderma of Jacobi poikilodermatomyositis of Petges, and calcinosis universalis.

The close relationship existing between the different forms of these two disorders is most forcibly demonstrated by the observation and analysis of the symptomatology There are abundant observations of transitional forms in confirmation of this relationship ranging from a benign form of scleroderma to calcinosis universalis, a malignant sequel of dermatomyositis.

Additional evidence of the relationship of scleroderma to dermatomyositis is the occurrence of acute polymyositis previous to the development of the acrosclerotic type of scleroderma. Cutaneous lesions of acrosclerosis may coexist with symptoms of dermatomyositis as reported by Talbott and his collaborators. The postmortem findings were "nonsuppurating dermatomyositis, scleroderma, calcinosis and endarteritis obliterans of the kidneys.

Scleredema adultorum is closely related to generalized scleroderma. The development of the edematous process toward generalized sclerosis occurred in a recent patient of mine In several reported cases an attack of scleredema preceded the development of frank acrosclerosis.

The patient who developed generalized scleroderma following an attack of scleredema is now showing symptoms of muscular and nervous involvement typical of dermatomyositis

These observations speak strongly for the close relationship between scleroderma and dermatomyositis.

An analysis of the material exhibited in this contribution inclined me to believe that the symptoms of generalized scleroderma and related forms of scleroderma as well as of dermatomyositis represent reactions of hypersensitivity to infection, often chronic in nature. It is sometimes difficult to establish the infectious agent in the individual case. Tonsils and teeth are the most common sources of infection.

The infectious agent, according to the concept of etiology and pathogenesis advanced in these pages, acts upon the blood vessels, particularly the arterioles of the peripheral vascular system, to induce arteriolar spasm. Occurring concomitantly with arteriolar spasm, there may be other signs of primary vascular involvement such as purpuric, telangiectatic, gangrenous, or ulcerating lesions.

The vascular changes, at first functional then structural, produce degeneration of the extracellular elements and other components of the connective tissue.

Other hypersensitivity factors beside infection which are capable of precipitating vasospasm were commented on previously Briefly these are sera, vaccines, emotional stress and any of several agents responsible for associated allergic dermatoses occurring not infrequently in patients with scleroderma or dermatomyositis.

In this connection, the association of carcinoma of the female genital system and breast with dermatomyositis is interesting This was observed in 15.4 per cent of my patients with dermatomyositis. This incidence of concomitant malignant disease approximates that of Curtis.

Successful treatment of scleroderma and dermatomyositis depends on the establishment of the infectious agent or other hypersensitivity factor or factors responsible for the condition in the individual case.

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35

Cutaneous Manifestations of Diseases of Lipid Metabolism

By

Samuel J Zakon and Harry F Weisberg

THE MODERN dermatologist must be acquainted not only with the cutaneous morphologic forms of diseases of the skin and the histopathologic picture of these lesions but also with the under lying metabolic disturbances that may be responsible for the cutaneous eruption. This applies especially to those dermatoses in which an understanding of the metabolism of the lipids is essential. Hence a brief resume of our present knowledge of the chemistry and physiology of lipids will precede our discussion of the clinical entities.

THE BIOCHEMISTRY AND PHYSIOLOGY OF LIPIDS

Lipide is the generic term for fat and includes not only the true fats or triglycerides but other substances which are related to the fats by common physical or chemical properties. Despite the correct spelling as lipide, the medical literature has used the spelling lipid we shall conform to the latter Confusion has also resulted from the use of the terms lipoid and lipin(e) The term lipoid is applied to all substances which, in their general chemical and physical properties and especially in their solubilities, resemble the fats the term lipin(e) has been used to refer to substances of a fatlike nature, containing fatty acids and other groups with nitrogen and phosphorus (compound lipids) The term phosphatide or phospholipid(e) designates phosphoric acid-containing lipids these are compound lipids.

From the chemical point of view lipids are more diverse as a class than proteins and carbohydrates with which they are combined to form the constituents of animal and plant tissues. Lipids lack a specific linkage or specific groups they contain more elements and more reactive groups than carbohydrates or proteins Any organic substance capable of being metabolized by a living organism may be classified as a lipid if it is insoluble in water but relatively soluble in fat-solvents. Lipids are actual or potential esters of fatty acids and ordinarily must be utilized by living organisms they are classified according to their solubility and biologic relationships.

I Simple lipids. These are esters of fatty acids with various alcohols containing only carbon, hydrogen, and oxygen. They are nonpolar compounds and therefore insoluble in water or other polar solvents (alcohol) they are readily soluble in solvents which are themselves nonpolar (ether chloroform, or benzene) and are acetone-soluble

1 Glycerides (fats and oils) or neutral fats or true fats, such as esters of fatty acids with glycerol (butter fat)

2. Waxes such as esters of fatty acids with any alcohol other than glycerol (beeswax) The alcohol is usually of a relatively high molecular weight (cholesterol) Cholesterol esters (cholesterides) are found in blood plasma and in sebum.

II Compound lipids. These are esters of fatty acids with alcohols and also contain other groups They contain nonpolar hydrocarbons (fatty acids and/or sphingol) and highly polar fragments such as phosphoric acid, choline ethanolamine, inositol, galactose, or combinations thereof They are insoluble in acetone

A. Phospholipids or phosphatides are esters of fatty acid with alcohols and contain phosphoric acid and a nitrogenous base. The three principal classes of phospholipids found in animal tissues are lecithin cephalins and sphingomyelin.

1 Glycerophosphatides or phosphoglycerides are phospholipids in which glycerol is the only alcohol present.

a. Phosphatidic acids consist of glycerol combined with phosphoric acid and two molecules of fatty acid

b Lecithin or phosphatidylcholine is the most common phos-

pholipid, consisting of glycerol combined with two fatty acid molecules and phosphoric acid to which the choline radical is attached by an ester linkage. Contains two polar groups—phosphoric acid (anion) and choline (cation) Choline is a derivative of ammonium hydroxide, being a highly basic nitrogen-containing alcohol. The strong basicity is due to the fact that the nitrogen is fully methylated, existing as the quaternary positive charged NH_4 ion instead of NH_3 group Thus lecithin is soluble in ether and alcohol, being more soluble in water than neutral fats, they can act as emulsifiers for neutral fats

c. Cephalins occurring as lecithin, consist of glycerol esters but have choline replaced by a different nitrogenous compound. Cephalins are soluble in ether but insoluble in alcohol. Typical cephalins are phosphatidylethanolamine, which contains ethanolamine radical, and phosphatidylserine, which contains the amino acid, serine.

d. Lysophosphatides, including lysolecithin and lysophosphatidylethanolamine.

e. Acetal phosphatides.

f Phosphatides of tubercle bacillus.

2. Phosphosphingosides are phospholipids in which glycerol is replaced by the complex amino alcohol, sphingol. They consist of sphingol, fatty acids, phosphoric acid, and choline, and are very polar phospholipids, having phosphoric acid (anion) and quaternary positive charged NH_4 cation from the choline and an additional NH_3 group· thus they are insoluble in ether and soluble in alcohol. Sphingomyelin belongs in this group

3. Lipositols are esters of glycerol and fatty acids containing phosphoric acid, inositol, galactose, and an amine. Insoluble in alcohol.

B Galactolipids or glycolipids or cerebrosides consist of a high molecular weight fatty acid, sphingol, and a monosaccharide such as galactose or glucose· they do not contain phosphoric acid, and they are differentiated by the kind of fatty acid present.

1. Kerasin contains normal lignoceric acid. Normally the carbohydrate in kerasin is galactose· in Gaucher's disease, glucose is the major carbohydrate component.

2. Phrenosin or cerebron contains a hydroxylignoceric acid.

3. Nervon contains an unsaturated homologue of lignoceric acid which is called nervonic acid.

4. Oxynervon apparently contains the hydroxy-derivative of nervonic acid.

C. Sulfolipids are lipids containing sulfuric acid residue.

D Aminolipids and other insufficiently characterized compounds.

III Derived lipids. These are compounds derived by hydrolysis from the preceding two groups which may not have the general properties of lipids it is not necessary that they should have all of these properties.

A. Fatty acids are saturated or unsaturated and usually have an even number of carbon atoms exceptions are traces of fatty acids found in perspiration and sebaceous oil of scalp hair

B Alcohols such as glycerol, sterols or steroids. The old term, sterol, was originally coined to denote a cyclic monohydroxy alcohol of high molecular weight. The sterols of physiologic importance have proved to be monohydroxy alcohol derivatives of a cyclopentanoperhydrophenanthrene nucleus. The newer term, steroid, is the general name for compounds related to this nucleus Some other members of this group, in addition to the sterols cholesterol and ergosterol are bile acids, sex hormones, Vitamin D adrenal cortical hormones saponins, digitalis glucosides, and certain toad poisons.

Cholesterol esters were included under the waxes. The bile acids consist of cholic acid and, to a lesser extent desoxycholic acid and chenodesoxycholic acid they are formed in the liver from cholesterol. Cholic acid is combined with glycine or taurine to form the respective conjugated bile acids glycocholic acid and taurocholic acid. Taurine and glycine are highly polar and therefore oil insoluble and water soluble Thus the bile acids or their ionized bile salts can easily form emulsions in an oil and water mixture since the taurine (or glycine) end is immersed in the water and the phenanthrene nucleus is immersed into the oil phase

C Hydrocarbons are compounds such as squalene which accumulate in the liver of some animals (shark) they were recently demonstrated in human skin.

D Nitrogenous bases, including choline, ethanolamine, sphingosine, and serine.

TABLE 1
NORMAL SERUM OR PLASMA LIPIDS (MODIFIED FROM HOFFMAN)

Constituent	*Average*	*Range*
Total lipids	570 mg./100 ml.	340–820 mg./100 ml.
Total fatty acids	13 mEq./L.	7–20 mEq./L.
As stearic acid	366 mg./100 ml.	198–568 mg./100 ml.
Lipid phosphorus	9 mg./100 ml.	6–15 mg./100 ml.
As lecithin	234 mg./100 ml.	156–390 mg./100 ml.
As phospholipid fatty acids	5.8 mEq./L.	3.8–9.6 mEq./L.
Total cholesterol—Adults	194 mg./100 ml.	107–320 mg./100 ml.
Total cholesterol—Newborn infant	—	80–90 mg./100 ml.
Ratio (in adults) Total cholesterol / Lipid phosphorus	22	14–27
Cholesterol fatty acids	3.4 mEq./L.	1.9–5.8 mEq./L.
Cholesterol esters	135 mg./100 ml.	75–225 mg./100 ml.
Ratio (in adults) Cholesterol esters / Total cholesterol	70%	60–80%
Neutral fat	109 mg./100 ml.	87–450 mg./100 ml.
As fatty acids	3.8 mEq./L.	1.3–15 mEq./L.

Not all of the lipids contained in the blood can be determined routinely The tests which can be done without special techniques are total lipids (TL) total fatty acids (TFA) lipid phosphorus (P) total cholesterol (TC) and cholesterol esters (CE) The other lipid fractions are calculated by utilizing arbitrary assumptions.

The total lipids (TL) are determined by extracting the serum with hot alcohol and ether the filtered solution is evaporated to dryness, the residue extracted with petroleum ether and the extract evaporated to constant weight. The value of TL in the normal adult, in the postabsorptive state, is about 570 mg per 100 ml. (range 340–820 mg per 100 ml.) The test will reveal the presence or absence of lipemia, is used in fat tolerance experiments and gives some idea of the overall picture of lipid metabolism

All the fatty acids in the blood are present as esters. To determine the total fatty acids (TFA) the extracted lipids are hydrolyzed, liberating the fatty acids which are titrated with alkali One milliliter of N alkali will neutralize 1 mEq of fatty acid. The normal value of TFA in the adult is about 13 mEq

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B Alcohols such as glycerol, sterols or steroids. The old term, sterol, was originally coined to denote a cyclic monohydroxy alcohol of high molecular weight. The sterols of physiologic importance have proved to be monohydroxy alcohol derivatives of a cyclopentanoperhydrophenanthrene nucleus. The newer term, steroid is the general name for compounds related to this nucleus Some other members of this group in addition to the sterols cholesterol and ergosterol are bile acids sex hormones, Vitamin D adrenal cortical hormones saponins, digitalis glucosides and certain toad poisons.

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born infants the TC level is very low 80 to 90 mg per 100 ml., in the first few months of life there is a rapid rise, especially of the esters, to reach the lower limit of the adult range. At average normal cholesterol concentrations, the ratio of total cholesterol to lipid phosphorus (TC/P) is fairly constant in the adult, being equal to 22 (range 14–27) In conditions with a low total cholesterol, the TC/P ratio falls very quickly· however if the total cholesterol is increased, the TC/P ratio tends to rise, but slowly

In the Bloor method of determining the cholesterol esters (CE) the free cholesterol is precipitated with digitonin and the esters extracted with petroleum ether Some error is present with this method since not all of the esters are extracted with petroleum ether and some of the free cholesterol can be extracted. In the Schoenheimer-Sperry method the esters are hydrolyzed and the cholesterol is isolated as the digitonide. The CE are usually reported as the ratio of the esters to the total cholesterol (CE/TC) The average is about 0 70, or 70 per cent, the range with the Schoenheimer-Sperry method is 0 60 to 0 80 or 60 to 80 per cent and 55 to 75 per cent by the Bloor method. The CE are also reported as cholesterol fatty acids (CFA) for the calculation of other lipid fractions. Since the molecular weight of cholesterol is 387 the conversion formula is

$$\text{CFA(mEq/L.)} = \text{CE (mg/100 ml.)} \times {}^{10}/_{387}$$

The neutral fatty acids (NFA) are calculated from the values of TFA, PFA, and CFA, *ignoring the small amount of fatty acid* present in the cerebrosides the formula is

$$\text{NFA(mEq/L.)} = \text{TFA} - (\text{PFA} + \text{CFA})$$

To determine the neutral fat (NF) as fat, the value of 860 is ascribed as the molecular weight for neutral fat, therefore, each milliequivalent of neutral fat (860 mg.) will have 3 mEq of fatty acid. Thus the formula is

$$\text{NF(mg/100 ml.)} = \text{NFA(mEq/L.)} \times /_{10} \times {}^{860}/_{3}$$

It should be realized that the value for neutral fatty acids (NFA) and neutral fat (NF) is derived by calculation from

three separate determinations, along with certain assumptions. By "formula calculation" the upper limit of the normal range for NFA should be about 5 mEq per liter yet some apparently normal persons have values of nearly zero and others may have a calculated NFA value of 15 mEq per liter Such extreme values demonstrate that the empiric factors may be absurd, depending upon the summation of errors from the various assumptions. It would appear however that of the TFA, about 40 per cent are usually present as PFA and the remainder divided between CFA and NFA with only a trace of cerebrosides being present.

Lipoproteins probably occur in every living cell they need not necessarily contain phosphatides the lipids being linked with a great variety of proteins. The term liproprotein refers to a substance whose biologic and physical properties differ from the sum of the properties of its constituents.

In normal blood plasma, the lipid constituents are approximately: cholesterol esters, 33 per cent, free cholesterol, 8 per cent, phospholipids, 33 per cent, and neutral fats 26 per cent. The blood lipids are complex in nature and heterogeneous in their chemical behavior for instance, fatty acids neutral fat, cholesterol, and cholesterol esters are hydrophobic whereas the lecithin and cephalin phosphatides are hydrophilic.

Lipids are present in all fractions of the blood proteins but are concentrated in the alpha and beta-globulin fractions. The beta globulin fraction contains a lipoprotein which is designated as "X-protein or "beta₁ lipoprotein." The beta lipoprotein contains about 8 per cent by weight of free cholesterol, 39 per cent cholesterol esters and 29 per cent phosphatides. It has been estimated that 75 per cent of the serum cholesterol is present in this lipoprotein. The various lipoproteins constitute the transport system for at least 95 per cent of the major serum lipids (glyceryl esters cholesterol, cholesterol esters, fatty acids, and phospholipids) Human serum and the serum of various experimental animals contains a "spectrum of lipoproteins"—a series of substances containing different lipids combined with protein having a very wide range of molecular weights and hydrated densities. The lipoproteins vary in density because of their different lipid protein ratio Pure chylomicrons contain chiefly

neutral fat and have a density less than that of water Lipoprotein-complexes are giant molecules with a molecular weight above 1,000 000 and contain cholesterol, phospholipids, proteins, and possibly free fatty acids These large compounds have a low density but are slightly heavier than pure water The hydrated density of lipoproteins ranges from less than 1.0 gm. per milliliter up to 1.145 gm. per milliliter· the hydrated density of serum proteins is approximately 1.3 gm. per milliliter

Ultracentrifugation is used to study the rate of sedimentation of substances heavier than the medium in which they are suspended or dissolved. The lipoproteins are separated by different types of preparative ultracentrifugation, using a solution density of 1.063 gm. per milliliter (5 ml. of serum with 4 ml. of an aqueous solution of sodium chloride having a density of 1.1315 gm per milliliter at 20° C.) separates a whole series of lipoproteins (ranging in density from less than 1.0 gm. per milliliter up to 1.04 gm. per milliliter) from the more dense lipoproteins and the serum proteins. Subjection of the separated lipoproteins to analytical ultracentrifugation yields a film record from which can be determined the lipoproteins and their concentrations.

Ultracentrifugation can also be used to study the rate of flotation of substances lighter than the medium thus the lipoproteins show different rates of flotation when ultracentrifuged in salt solution Lipoproteins of the S_f 3–8 class, having a relatively slow rate of flotation and density of about 1 03 are present in the plasma of all persons. The S_f 3–8 fraction has a relatively high concentration of proteins and a low concentration of cholesterol, while the S_f 10–20 fraction contains little protein, much phospholipid and about 30 per cent cholesterol, it has a density of 1.01 and a faster flotation.

This fraction is seldom found in the plasma of normal young persons· when found it is more prevalent in males. The greater the serum cholesterol concentration, the greater the tendency towards an increased concentration of the S_f 10–20 fraction, there is no constant relationship, however for many persons with normal serum cholesterol levels have been found to have significant amounts of the S_f 10–20 complexes The incidence of the S 10–20 fraction has been found to be higher in the plasma of

young diabetics in persons over 40 years of age and, compared to similar age groups, much higher in patients with recent coronary occlusion. Though the evidence is not conclusive, a fairly good correlation has been demonstrated to exist between the presence of considerable amounts of S_f 10–20 lipids and the development of atherosclerosis.

Most of the plasma cholesterol (more than 90 per cent) is carried in the form of lipoprotein complexes this function is dependent upon the association of cholesterol and plasma proteins primarily the alpha and beta globulins. It is very probable, therefore, that the ratio of cholesterol to protein in the lipoprotein molecules increases with increasing hypercholesterolemia. Heparin and other substances can affect or alter the structure of the lipoprotein spectrum resulting in the clearing of lipemic plasma. The level of plasma cholesterol will depend upon the absorption of exogenous cholesterol, the endogenous synthesis of cholesterol, the excretion of cholesterol, and the destruction or metabolism of cholesterol.

Exogenous cholesterol is absorbed slowly over a period of days the acute ingestion of excess cholesterol may at times, lead to a slight increase of the plasma cholesterol level. Chronic ingestion of cholesterol in some animals will lead to hypercholesterolemia, it is questionable if the effect is a direct one or secondary to alteration of the physico-chemical state of the plasma cholesterol after changes in intake of fat or cholesterol. A decreased intake of fat results in decreased absorption of cholesterol an excess of bile salt (cholate) increases the absorption and the absence of bile decreases the absorption of dietary cholesterol. Other factors which may contribute to the absorption of cholesterol are the dynamics of the bowel itself possible interference by other dietary substances (eggplant artichoke leafy vegetables and fruits) and the relation of the amount of cholesterol excreted by the intestinal wall.

Cholesterol is easily synthesized in the body from 2-carbon fragments (acetate) or short-chain fatty acids squalene has been suspected to be an immediate precursor of cholesterol. Practically every organ with the possible exception of adipose tissue and adult brain tissue can synthesize cholesterol How

ever the liver is the only organ supplying significant amounts of cholesterol to the plasma and thus serves as the actual source of plasma cholesterol. Although the liver furnishes the cholesterol found in the blood, it does so at a rate that is not easily or rapidly changed, moderate changes in the rate of synthesis therefore, do not necessarily induce similar changes in the level of plasma cholesterol.

Significant quantities of unchanged cholesterol are eliminated from the body via intestinal excretion. The cholesterol in bile is a secretory product of the liver Urinary excretion of cholesterol, in the absence of renal disease, is negligible. Fecal cholesterol is the sum of the nonabsorbed dietary cholesterol plus cholesterol excreted by the intestinal wall, the major portion of such intestinal excretion occurs in the small intestine. Decreased excretion of cholesterol via the intestinal wall rarely results in a high plasma cholesterol even though a rare type of idiopathic hypercholesterolemia associated with little fecal excretion of sterols has been reported. Byers and his associates report that an extremely high level of plasma cholesterol or an increased rate of endogenous cholesterol synthesis results in an increased fecal excretion of cholesterol and coprosterol.

Cholesterol is broken down in the body at least one of the products being cholic acid, various experiments have shown that cholesterol can also be converted to glycogen, fat, carbon dioxide, and progesterone. From the animal work of Byers and his associates it seems that the injection of physiologically emulsified cholesterol (in the form of hypercholesterolemic serum) results in a disappearance from plasma in 12 to 24 hours the cholesterol is found primarily in the liver from which it gradually disappears over a period of several days. The major portion of such injected cholesterol is converted in the liver to cholic acid and excreted in the bile experimental biliary obstruction or anastomosis of the bile duct to the inferior vena cava resulted in a very rapid rise of plasma cholesterol, associated with a rise in plasma cholate.

It seems fairly evident that the processes of intestinal absorption and the excretion of cholesterol do not play a major role in the control of the plasma cholesterol level. The liver

however is very important for it is the site of the synthesis and destruction of the cholesterol. The destruction or conversion (metabolism) of cholesterol by the liver is the primary factor in controlling the plasma cholesterol level, only the almost complete absence of synthesis, as might occur in severe hepatocellular damage, will affect the plasma cholesterol level.

Hypercholesterolemia will therefore result if the liver is unable to remove cholesterol from the blood and subsequently metabolize the cholesterol. This may occur because physicochemical changes in the blood make cholesterol unavailable to the liver or the liver may be able to remove cholesterol from the blood but be unable to metabolize it, resulting in increased deposition within the liver and later spilling back into the plasma In most cases the failure of the liver is due to the former mechanism. In hepatocellular disease there is an accumulation of bile salts which results in increased adsorption of cholesterol by the normal plasma proteins in the nephrotic syndrome, however there is a reduction of the albumin and the total protein content but the alpha and beta globulins are markedly increased, such changes in the globulins resulting in increased adsorption of cholesterol by the total protein complexes.

DISEASES OF LIPID METABOLISM OF INTEREST TO THE DERMATOLOGIST

Lipidosis is the general term applied to a group of diseases characterized by the accumulation of large, lipid-containing cells (originating from the reticuloendothelial system) and by unknown etiology The term lipoidosis includes the diseases of lipidlike alterations unfortunately this term has replaced, to a great extent, the term lipidosis in the clinical literature Though not all of the features must be present to establish a diagnosis, each disease has characteristic clinical, chemical, and pathologic features The lipid deposited in xanthomatosis is cholesterol and its ester in Gaucher's disease kerasin in Niemann-Pick disease sphingomyelin and in disseminated lipogranulomatosis, a mixture of fatty acids neutral triglycerides and phosphatides.

The infiltrated tissues may take on the appearance of tumors and are called xanthomas since they often have a yellowish color

apparently due to dissolved carotenoid substances. The xanthomatoses are the most important clinical group. Many investigators believe that the reticuloendothelial proliferation in xanthomatosis is primary and that the cholesterol deposition is secondary there is a tendency therefore, no longer to consider the various forms of xanthomatosis as a primary disturbance of lipid metabolism.

PRIMARY ESSENTIAL LIPIDOSES

The serum lipids are usually normal and the lipids which accumulate in the cells are lipids other than cholesterol. The cellular accumulation is presumably due to a cellular abnormality involving increased synthesis or decreased utilization of the lipid by the particular cells involved. In the following group of primary essential lipidoses, only the cutaneous manifestations will be considered in detail.

A. Gauchers disease. This disease may occur at all ages it is the commonest of the primary lipidoses. About one-third of the cases recorded in the literature can be regarded as familial, once the disease is established, it is believed to be transmitted as a simple dominant trait. An individual affected by the trait has a disturbance of lipid metabolism resulting in the accumulation of kerasin, in which the normal galactose component is replaced by glucose. No typical cases have been described in association with xanthomas

In the chronic form of the disease, the skin often becomes dull brown or yellowish especially on the exposed parts of the body Pingueculae (yellowish, wedge-shaped thickening of the conjunctivae at the corneoscleral margins) are commonly seen in adults and usually lacking in children. A hemorrhagic diathesis is usually present along with hypochromic anemia, leukopenia, and thrombocytopenia.

Treatment is purely symptomatic.

B. Niemann-Pick Disease This metabolic disease occurs in infants some authorities state that females are affected more often than infant boys (6 to 1) but Van Crevold states that both sexes are equally affected. In addition to the characteristic generalized symptoms, there is a peculiar yellowish hue to the skin without

any deposition of lipid in the skin, cutaneous xanthomas are a very infrequent finding

The pathologic changes and symptomatology are due to the accumulation of reticuloendothelial elements (histiocytes) which are infiltrated with lipid, sphingomyelin in almost all organs but mainly in the spleen, liver bone marrow and lymph nodes. The accumulation of lipid is mainly sphingomyelin glycerophosphatides are also increased but to a lesser extent and cholesterol and cholesterol esters may also be present. If neurologic symptoms are present, one must consider the acute form of Gaucher's disease; idiopathic lipemia or idiopathic familial lipemia with hepatosplenomegaly may be difficult to differentiate from Niemann-Pick disease. Aspiration and demonstration of the typical Niemann-Pick foam cells establish the diagnosis

No treatment has been successful.

C. **Tay-Sachs Disease.** Amaurotic family idiocy is the term applied to a number of diseases differing clinically but having certain features in common familial incidence, idiocy neurologic symptoms and, frequently an affection of the optic nerve or retina.

The first sign is apathy followed by poor vision or blindness; as the disease develops, the hearing becomes abnormally acute the slightest noise startling the apathetic, drowsy child. Bursts of explosive laughter occur later and the entire process slowly develops to a state of idiocy In the last months of life the skin of the palms, soles, and legs may show patches of canary yellow pigmentation and thickening Death usually occurs from an intercurrent infection the patient rarely lives beyond age three

The visual disturbance is related to the optic atrophy and the finding of a cherry-red circular spot surrounded by a grayish-white zone in the macular region of both eyes. Some cases of Niemann-Pick disease have been described with practically the same cherry red spot.

The blood picture is normal, however there is an accumulation of lipid in spleen, brain liver and lymph nodes. The sphingomyelin content of the brain is markedly reduced the cells show an increased deposition of a galactoside with neuraminic acid greater than that seen in Niemann Pick disease.

D Disseminated lipogranulomatosis. In Farber's opinion, this congenital disorder of lipid metabolism is most closely related to Niemann-Pick disease. The spleen, heart, liver and lungs show an increased total lipid content, the lipids consist of fatty acids, neutral triglycerides, and phosphatides (the greater part presumably being sphingomyelin)

The disease is recognizable at birth or shortly thereafter being characterized by a hoarse cry feeding difficulties respiratory difficulty and widespread involvement of the joints and periarticular tissues the last is so extensive that a diagnosis of rheumatoid arthritis has been made. Another feature of the clinical picture is pigmentation of the skin.

E. Lipochondrodystrophy or Gargoylism. Recent evidence has led to the opinion that this disease results from a disturbance of mucopolysaccharide metabolism, since mucopolysaccharides play an important part in the physiologic upbuilding of connective tissue such a disturbance could explain the prevalence of skeletal deformities in gargoylism

The differentiation of a forme fruste of gargoylism from sporadic cretinism may be difficult and from Morquio's disease (osteochondrodystrophia deformans) very difficult, if not impossible Gargoylism may be distinguished from cretinism by the type of bone deformities, absence of retarded ossification, absence of myxedema, and the normal blood cholesterol

XANTHOMATOSES

The xanthomatoses are a group of diseases having the common characteristic of a proliferation of the reticuloendothelial elements with the formation of granulomatous tissue in various organs and the formation of large pale foam cells containing cholesterol and cholesterol esters Many classifications of the xanthomatoses have been presented, they may be divided roughly into two major groups:

Primary essential xanthomatoses. This is a group of diseases of unknown etiology in which the xanthomas bear no direct relationship to the concentration of serum lipids. Primary xan-

These lesions may be the first sign of developing cardiovascular disease and in about 30 to 40 per cent of cases may be associated with various aspects of severe cardiovascular disease. Xanthelasma may also be associated with diabetes mellitus and/or hepatic disease. It is often encountered in patients with leprosy

Xanthoma tuberosum is most common in young adults but may be seen at any age The lesions consist of yellow to brown papules nodules nodes, or tumors Infiltrated plaques, striae, or nonelevated, smooth, flat areas may predominate on the ex tensor surfaces Yellowish plaques may also be seen on the palms, soles, axillae, and in the tendon sheaths and synovial membranes.

The tendon xanthomas are intimately connected with the tendon itself the overlying skin is not involved and not discolored and thus can be differentiated from the subcutaneous nodules of rheumatoid arthritis

Coronary artery and valvular heart disease (due to xanthoma formation) may be seen in adults and children the prognosis is poor when there is cardiovascular involvement. The elevated serum cholesterol may be the only finding, it may herald the later onset of coronary artery disease The other members of the family should be examined only the skin tendons, or the blood vessels may be involved in members of the same family

Hereditary xanthomatosis is not a rare disorder Adlersberg studied 201 patients related to families having xanthoma and found 69 per cent to have marked elevations of the serum cholesterol, 49 per cent had the full blown syndrome (i e hypercholesterolemia, coronary heart disease and skin xanthoma) 40 per cent had coronary heart disease 30 per cent had only xanthelasma, and 12 per cent had the single finding of xanthoma tuberosum or xanthoma tendinosum Barr and his associates have recently reported the finding of aortic stenosis with calcification in hypercholesterolemic xanthomatosis

Many attempts have been made to decrease the cholesterol and other lipids of the blood to prevent the recurrence of atherosclerosis it seems that a low caloric diet is more important than a low fat diet and is easier for the patient to maintain

Histopathology The histopathologic changes of xanthoma with well developed nod[illegible] are typical and diagnostic and con

sist of many foam or xanthoma cells in intimate relationship with capillaries and smaller blood vessels in the upper part of the cutis frequently with a varying number of Touton giant cells. The Touton giant cells are characterized by the arrangement of their nuclei in a complete circle surrounded by deposits of lipids in the cytoplasm. Polariscopic examination reveals double refractile cholesterol crystals.

The endothelial cells of the walls of the smaller capillaries also participate in forming xanthoma cells The xanthoma cell is generally conceded to be a histiocyte and a cell containing lipids rather than a true tumor cell. In involuting lesions, fibrosis takes place and areas of cholesterol clefts are seen. A deposition of calcium is rarely found.

The histologic features of xanthoma planum are similar to those of xanthoma tuberosum with the exception that there are relatively few Touton giant cells to be found. As the lesions become older the fibrosis increases, and the lipids decrease. The histologic appearance of xanthoma tuberosum in the fibrotic stage may closely simulate the histologic picture of histiocytoma, including intra- or extracellular deposit of hemosiderin and lipids.

The tendinous xanthomas are interwoven with the tendon tissue· the foam cells and fibroblasts are found in a closely-bound fibrous mat. Only small numbers of giant cells, leukocytes, and lymphocytes are seen.

Laboratory findings. The serum is clear and transparent. The total fatty acids are increased, due to the increase of total cholesterol and phospholipids thus the total lipid level of the serum is increased. The total cholesterol is increased 2 to 5 times, and the cholesterol esters are increased proportionately so that the percentage of esters is normal. The lipid phosphorus may be slightly elevated or normal, the neutral fat may be low normal, or slightly elevated.

B Normocholesterolemic type or reticuloendothelioses. This group of diseases does not have an elevation of the serum cholesterol. Cholesterol can accumulate in the cells without an elevated serum cholesterol, on the supposition that the reticuloendothelial cell can synthesize more cholesterol. Recent observations support the concept that Hand-Schueller-Christian disease, Letterer

Siwe disease, and eosinophilic granuloma are all variations of a single disease process. They are nonfamilial granulomatous lesions possibly infections, with secondary deposition of cholesterol. The process may be generalized, involving the skin, bones brain, meninges, lungs pleura, lymph glands, liver and spleen this may be seen primarily in infants (Letterer Siwe disease) Various organs may be involved, resulting in the Hand Schueller Christian syndrome or the disease may be evident in a monosymptomatic form, e.g involving only bone (eosinophilic granuloma of bone) or skin (xanthoma disseminatum)

1 *Letterer-Siwe disease* Though the disease is primarily a nonlipoid histiocytosis lipid (cholesterol) deposits may be found as a secondary phenomenon. Those affected are usually children under two years of age the course is rapidly fatal. The onset in most cases is acute the signs and symptoms consist of splenomegaly lymphadenopathy granulomatous foci in bones hepatomegaly purpura, fever anemia, skin rash, and visceral lesions (lung) Even though the liver is involved jaundice and ascites are not present. Some acute cases of this disease have been reported in which xanthomatous transformations were observed before death of the infant.

2. *Hand Schueller-Christian disease* The disease has its onset in children between the ages of two and five years often becoming manifest after an infectious disorder The disease has a chronic, protracted course ranging from months to years it is characterized by a triad of defects exophthalmos diabetes insipidus and cystic lesions of the cranial membranous bones. Xanthomatous lesions have also been found in other parts of the skeleton skin, and viscera. Serum cholesterol may be increased. Chronicity of the disease is indicated by the characteristic foam cells—histiocytes containing secondarily deposited cholesterol.

3. *Eosinophilic granuloma.* The disease is usually found in children, mainly boys, under the age of six, and is rarely seen after the age of 30 the course is relatively benign. Eosinophilic granuloma may occur in the skeleton (eosinophilic granuloma of bone or osseous granuloma) skin (xanthoma disseminatum) liver kidneys brain, lung, and gingival mucosa. The focal

affections may be solitary or multiple· local pain over the lesion is a prominent feature. Bone destruction may be found anywhere in the skeleton except the hands and feet. The most frequent sites are skull, costal vertebrae, mandibles, and pelvis, the bones show radiolucent areas with cortical expansion. The number of eosinophils in the blood is usually but not always increased and leukocytosis may be present, the values of cholesterol, cholesterol esters, calcium, inorganic phosphorus, and alkaline phosphatase are normal.

The skin lesions are lemon or chamois colored and later may be maroon. They are distinguished from the skin lesions in hereditary xanthomatosis by the color and location. In xanthoma disseminatum the lesions are disseminated over the entire body with the preferred locations being in the axillae, about the neck, face, eyelids, and antecubital fossae; they may also be noted as flat or tuberous xanthomas on the scalp or in the mucous membranes of the mouth or bronchi. The lesions are raised, discrete, or clustered in smooth patches or arranged in ridges and furrows, varying from pinhead to walnut size. They do not ulcerate and may disappear in later life.

Xanthoma disseminatum has erroneously been classified as nevoxanthoendothelioma in infants, the latter lesion is a discrete, orange-brown disseminated xanthoma. The skin lesion may be petechiaelike rather than the disseminated variety and may occur together with fully developed xanthomas. These petechiae" are flat, reddish-purple, and of pinhead size; they may disappear leav ing a brownish spot.

In some cases, the lesions are seen as yellowish tissue in the sockets of the teeth they may simulate an accumulation of pus at the root of the tooth.

X-ray therapy has been effective, especially for the bone lesions. The administration of para-aminosalicylic acid (2 to 4 grams per day) may at times, favorably influence the skin and subcutaneous lesions.

II. Secondary Xanthomatoses

A. Liver disease

1 *Xanthomatous biliary cirrhosis* This condition is presum ably due to the obstruction of the bile ducts by the xanthomas. The etiology is unknown and the disease is not hereditary a

distinction from hereditary xanthomatosis. Histologic studies of liver biopsy and postmortem material have revealed that this condition is a primary liver disease with secondary hypercholesterolemia and not a primary xanthomatosis. Thannhauser states that the condition is seen only in women if it is suspected in a man, another type of liver disease should be looked for

The disease progresses slowly itching and jaundice being the first symptoms The jaundice is chronic and may be of several years duration The obstruction of the bile ducts, however is never complete for urobilin is always present in the stool and urine Xanthoma planum and tuberosum are found soon after jaundice develops appearing over the entire body including the creases of the hands Hepatosplenomegaly develops and spider angiomas may be seen, death ensues within four to seven years after the onset due to bleeding from the esophageal varices

The serum is clear and transparent. The total cholesterol and lipid phosphorus are increased (6–10 times normal) even more than in hereditary xanthomatosis Thus the total lipids are increased, the neutral fat is normal or decreased. In the early stages the cholesterol esters are also increased proportionately and thus the percentage of esters is normal late in the disease, the decrease of the esters is greater than the decrease of the total cholesterol so that the percentage of esters falls below the normal range The S 6–8 lipoprotein fraction is increased. The fact that urobilin is always present in the stool and urine proves that the bile duct obstruction is not complete

2 *Hemochromatosis* Skin xanthomas in hemochromatosis occur but rarely The disorder is believed to be secondary to the liver damage (cirrhosis) involving the finest bile capillaries and resulting in excess formation and decreased excretion of cholesterol. In such a case therefore one would expect to see an elevation of the serum cholesterol but no increase of the neutral fat In the few reported cases however the neutral fat determination was not reported.

Xanthomas and xanthelasma may occur the skin has a blue-gray-brown color Cardiovascular involvement is not a prominent feature Diabetes is often present, and ascites may occur The prognosis is poor because of the fibrosis of the viscera.

The serum is clear and transparent. The total lipids are elevated due to the increased levels of cholesterol and lipid phosphorus the neutral fat is decreased. Serum bilirubin is elevated and hyperglycemia and glycosuria may be present. Hemosiderin may be found in the skin, viscera, and urinary sediment.

3. *Obstruction of Common Bile Duct* It is not uncommon to have an injury of the common bile duct during surgery resulting in obstruction of the bile duct and the development of hyper cholesterolemia. Thus the elevated serum cholesterol is due to the complete obstruction of the common bile duct. In rare instances, hypercholesterolemia may be sufficiently elevated to result in the formation of xanthomas.

Xanthomas, jaundice, and related symptoms (clay-colored stools) are present with the obstruction. There is a disappearance of the xanthomas and jaundice after the obstruction is removed. The cardiovascular system is not involved.

Serum is clear but bile-stained. The total fatty acids are elevated due to the increased cholesterol and phospholipids the neutral fat is decreased.

B. Hypothyroidism. The occurrence of xanthomas in myxedema is rare. Hypothyroid patients have an elevated serum cholesterol which reverts towards normal with thyroid medication. However even with an elevated serum cholesterol, hypothyroid patients have relatively normal levels of neutral fat and phospholipids.

C. Hyperlipemia

1 *Alimentary hyperlipemia.* Xanthomas do not occur in physiologic hyperlipemia after the ingestion of a meal rich in fat.

2. *Idiopathic hyperlipemia.* In this disorder a defect in removing fat from the blood results in a retention hyperlipemia. There may be an elevated serum cholesterol associated with hyperlipemia, thus the cholesterol may then infiltrate various tissue cells.

Lever and his associates reported several patients with idiopathic hyperlipemia who exhibited tuberous xanthomas, tendon xanthomas, and coronary heart disease, findings not previously reported. Thannhauser regards hyperlipemia of chronic pancreatitis as a disease entity stating that pancreatitis can cause

lipoma, xanthomatous polycystic lymphangioma, and epithelial tumors.

3. *Pigmented villonodular synovitis.* This term has been used to designate a widely diffuse xanthomatosis involving the synovial membranes of joints and tendon sheaths it has replaced the term "xanthomatous tumors of joints." Cholesterol and total lipid values of the blood may be within normal limits.

III. MISCELLANEOUS

A. Necrobiosis Lipoidica Diabeticorum This condition is characterized by single or multiple yellow to red plaques which vary in size and usually occur on the extremities. The border of the plaque is violaceous with a red or brown areola. The surface of the older plaques is usually traversed by fine telangiectatic vessels. The plaques are quite hard, especially along the borders. They are not elevated, but the center of the lesion may be depressed or even ulcerated. The lesions heal slowly with an atrophic scar and the process of healing may take years. The lesions are not scaly do not itch, and are not painful. The areas of predilection are the legs especially about the ankles Areas less often affected are the thighs, forearms, neck, face palms and soles

The disease is much more common in women than in men and may precede clinical diabetes, although generally diabetes mellitus precedes the skin lesions. High blood lipids, especially cholesterol, have frequently been found.

The histopathologic picture is described by Abulafia (see p. 59)

The disease is readily recognized clinically by the flattened plaques with yellowish centers surrounded by violaceous or red brown borders, with or without central ulceration and by the fact that it occurs in association with diabetes mellitus. The disease should be differentiated from cutaneous amyloidosis, morphea, erythema induratum sarcoid lipoid proteinosis and granuloma annulare

B Lipoid Proteinosis. This rare condition generally begins in infancy an inability to cry is noted and as the voice develops the child is unable to speak above a whisper Nodular and hyperkera

totic, verrucous and fibrous sclerosing lesions predominate on the face, extremities, and mucous membranes, including the larynx and pharynx. The tongue has a firm, almost woodlike, consistency and is bound down to the floor of the mouth. The mucous membranes of the lips exhibit yellowish white plaques and the vocal cords and the epiglottis are similarly involved. The face has a pock-marked appearance. Hypertrophic plaques are present on the elbows and knees simulating localized amyloidosis. Verrucous lesions are frequently seen on the fingers and feet. The color of the lesions is that of normal skin.

There is a hereditary tendency with a history of consanguinity of the parents and a familial tendency towards diabetes Blood lipids are essentially normal.

The histopathologic picture is described by Abulafia (*see* p. 59)

Lipoid proteinosis can be distinguished from other types of xanthomas involving the larynx and pharynx by the absence of typical lesions of xanthoma and by the absence of xanthoma cells histologically

C. Leukemic Xanthomatosis. Freud and his associates reported the case of a two-year-old Puerto Rican child with xanthomatous lesions. About one year later a chronic leukemic myeloid response developed, a year later biopsy of the lymph nodes revealed visceral reticuloendotheliosis. The patient died at the age of five years and three months necropsy revealed widespread reticuloendotheliosis with many primitive mesenchymal foam cells with high cholesterol content. It remains to be seen whether this is a distinct clinical and pathologic entity or coincidental leukemia in a child with primary xanthomatosis

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Sunlight and Skin Diseases in the Tropics

By

Hernan Corrales-Padilla

This report deals with disorders of the skin induced by sunlight in persons living in Honduras. The intensity of solar radiation in Honduras often causes cutaneous reactions which differ in type and in their response to treatment from those observed in other areas of the Americas.

Depigmentation of the face, neck, and upper arms is very common in my country where it is of considerable concern to women whose dark skin causes it to stand out prominently. Many of these depigmentations are associated with fungi and pyogenic organisms and are therefore called parasitic achromias. This is particularly the case in children. In other instances however depigmentation is directly due to the action of sunlight. Described independently by Schmidt in Costa Rica and called by him actinic spotted achromia, the disorder occurs both with and without lesions of solar dermatitis. It is strange that this disorder has received such scant consideration in the literature especially since it is one of the commonest reasons in tropical countries for dermatologic consultation.

Repigmentation is hastened in the actinic achromias by the administration of vitamin B complex fortified with thiamine riboflavin and nicotinic acid. Avoidance of sun and wind is naturally a necessity.

Vitiligo is also more common in the tropics than in the temperate zone. Looked upon as an exhaustion phenomenon induced by the action of intense sunlight this is readily understandable. Treatment with oral vitamins, as in actinic achromia, has proved more effective than any other therapeutic agent including products containing ammidin or xanthotoxin.

The occurrence of erythema, following a short exposure of the skin to sunlight, is common along the northern coastal lowlands of Honduras. Persons complaining of generalized itching when they come to the capital which lies at considerable elevation above sea level often give a history of a severe episode of solar erythema some months previously

Polymorphus light eruptions comprise the largest group of cutaneous reactions to sunlight. These eruptions vary in size from small, round, patches of erythema on the cheeks and nose to large, crust-covered areas of eczematous dermatitis involving the entire face, particularly around the mouth where they simu late areas of contact dermatitis. At other times, papular lesions typical of prurigo occur either scattered throughout the areas of eczematous dermatitis or discretely as independent elements of prurigo. No evidence of disturbance of porphyrin metabolism is found in these patients.

The papular and prurigolike types of actinic reactions start with pale-red, round papules on the face, V area of the chest, and extensor surfaces of the arms particularly the forearms. The skin lying between the affected areas appears normal except for occasional slight edema. The lesions usually erupt in the midst of summer sometimes in great profusion and at other times in small numbers. Scratching often leads to infection and the formation of pitted scars.

The occurrence of abdominal colic and diarrhea is not uncommon with severe attacks of solar dermatitis. In two patients with these symptoms the cutaneous lesions became aggravated by the ingestion of 6 gm of sulfadiazone, thus lending support to the concept that the sulfonamides are strongly photosensitizing.

In contrast with the findings of other observers, hyperpigmentation of affected areas is of frequent occurrence in Honduras.

I have not seen Negroes with solar dermatitis.

No conclusions concerning the possible participation of the endocrine glands in the production of solar dermatitis could be drawn from my series of cases.

The thickening of the skin of the ears and over the cheek bones together with the loss of eyebrows, in patients with severe attacks of actinic prurigo associated with itching, often

suggests the diagnosis of leprosy A profusion of papules and hemorrhagic crusts on the face can be quite repulsive looking Milder degrees of lichenification give a leathery appearance to the face resembling the condition known as farmer's skin.

In *histologic sections* one sees areas of hyperkeratosis and acanthosis with a moderate inflammatory infiltrate around the capillaries of the upper dermis. With appropriate stains, extensive basophilic degeneration of the collagenous fibers is found in advanced lesions of the disorder

Actinic dermatoses having both the clinical and histologic appearance as well as the localization of lupus erythematosus are very common in my country They differ however from chronic discoid lupus erythematosus in their response to treatment with either gold salts or quinacrine and in the fact that they heal quickly when the patient avoids the sun and takes nicotinic acid. Whereas the effectiveness of the gold salts and quinacrine is unquestioned in chronic discoid lupus erythematosus their action in patients with a similar appearing dermatosis is deleterious, the eruption usually worsening.

At times, the lesions resemble areas of erythema found in pellagra, but their response to avoidance of sunlight and treatment with nicotinic acid is as favorable as the response of those simulating lupus erythematosus I am in full agreement with Gougerot that we are dealing with an entity pathogenetically distinct from lupus erythematosus, a disease in which sunlight as a factor in its production is rapidly falling into disfavor particularly with North American dermatologists. Sunlight avowedly induces redness and burning of the lesions in many patients with lupus erythematosus but it probably is not important in its causation.

The occurrence of solar urticaria in Honduras is not uncommon. In a boy of 12, typical urticarial lesions occurred every afternoon about four o'clock. At the same time the boy felt very tired and without appetite These symptoms had persisted for two years when difficulty in breathing started. On questioning, the boy said that he played football every day between three and four in the afternoon in bright sunshine The eruption rapidly disappeared when he kept out of the sun.

temic symptoms and metabolic disturbances, they are a feature of a number of dermatoses associated with porphyrinuria.

It is when the coproporphyrin isomers are present in increased amounts together with the uroporphyrin isomers I and III and other porphyrins, that we speak of porphyria, which may be acute or chronic. Attacks of acute porphyria may be brought on by a variety of factors of which alcoholic debauches and the ingestion of large amounts of barbiturates or chloral hydrate are the main offenders. Systemic infections and lead poisoning can also bring on an attack. According to Borda, some attacks start with symptoms referable to the gastrointestinal tract, while others begin with symptoms of such nervous disorders as Parkinson's disease or ascending paralysis of Landry. Involvement of the skin, however, does not occur.

Chronic porphyria, on the other hand, is an inborn error of porphyrin metabolism sometimes associated with cutaneous lesions which usually appear later in life. Hydroa vacciniforme is one of two dermatoses universally associated with porphyria. It is characterized by crops of lesions consisting of small vesicles situated on an inflamed skin and limited to the face, ears, cheeks, and hands of the young, predominantly boys. Hypertrichosis may be present, and the teeth may turn chocolate brown. The color of the urine is usually dark red.

The disease is regarded as hereditary, but in a recent observation of two children, this was not the case. These children, one a boy of six and the other a girl of eight, live in the country. Their mother states that the eruption is more severe in summer, that no other member of the family ever had a similar eruption, and that the children showed no eruption until they were three and five years of age.

The other eruption associated with porphyria is bullous and erosive pigmented porphyria appearing in adults, to use the designation originally suggested by Borda. The characteristic features of this adult form of chronic porphyria associated with skin lesions were present in two patients recently observed. Both patients were men whose work compelled them to be exposed to the sun for several hours a day.

The first patient, a man of 35, stated that five years previously blisters began to appear on the back of his hands whenever he

worked in the sun. They continued to break out, especially during the summer months. On examination, the skin of the back of the hands appeared spotted with pigmentations, erosions and scars. The patient complained of headache and pain in the eyes upon exposure to sunlight.

During the past three years he noticed that the slightest injury to the skin produced blisters such as those induced by exposure to the sun. The blisters broke and healed with scars which caused deformities of several fingers No blisters were present at the time of the first examination, but one month later after resuming work, he presented blisters on the back of the hands and a vesicle on the ear lobe. The eyebrows and lashes were bushy and long, and the skin of the neck was thickened.

The urine varied in color during subsequent visits to the clinic. Although generally regarded as red or port wine in color the freshly voided urine of this patient was usually yellow Sometimes it remained yellow or brown on standing, and at other times it turned dark red. This observation is in agreement with that of Brunsting, Mason, and Aldrich.

The second patient was an 80-year old man who presented an ulcer 1 cm. in diameter on the upper lip, which proved to be basal cell epithelioma. In addition, there were several senile keratoses on the face, together with patches of colloid degeneration on the neck and in the axillae. Upon admission to the hospital, the patient complained of severe abdominal pain. The color of the urine became dark red within a few minutes after being voided and showed dark-orange fluorescence under ultraviolet light.

The presence of patches of colloid degeneration of the skin on the neck of this patient lends support to the concept of Borda and Pierini that colloid milium and colloid degeneration of the skin are caused by disturbances in pyrrole metabolism. They cite their own experience and that of Gonzalez who observed microscopic changes in material obtained from a patient with porphyria, changes similar to those described in colloid milium.

Porphyrinuria occurs in many skin diseases, usually associated with evidence of liver damage Pellagra, erythema multiforme, dermatomyositis, and lupus erythematosus are some of the disorders in which increased excretion of the coproporphyrin isomers has been reported.

Pellagra merits special consideration in this report due to its great frequency in Honduras. Studies carried on with the administration of vitamins to determine the part played by sunlight alone, as distinct from vitamins, in the production and exacerbation of pellagra proved inconclusive The explanation for this probably lies in the circumstance that most of the test subjects were alcoholics, vitamins being unable to exert their catalyzing action in the presence of alcohol.

It is probable that the quality of the food is the determining factor in precipitating episodes of pellagra. Because of severe soil erosion, scanty fertilization, and failure to rotate crops, the soil is deficient in both essential and trace minerals, a deficiency which lowers the nutritional value of corn rice, and beans which are the chief items of diet among the poorer classes. Also, very little fruit is eaten by the people

The influence of heat alone, as distinct from light, in the production of dermatoses appearing on exposed areas of the skin was recently emphasized by Borda. A man working in a glass factory where he was exposed to great heat from the furnaces, developed typical lesions of lichen planus on exposed areas of the skin. The lesions tended to disappear whenever he stayed away from work, flaring up on his return. I recently had occasion to observe a case of lichen planus in a similar worker Neither Borda's nor my patient was taking atabrine

Cutaneous lesions produced by more or less daily exposure to the sun and wind over a long period of time are common in Honduras. Epithelioma, basophilic and colloid degeneration, homogenization of the connective tissue and squamous-cell carcinoma comprise the bulk of these lesions.

TREATMENT

The use of oral nicotinic acid in doses of 100 mg four times daily together with avoidance of exposure to sunlight and wind has proved effective in the management of acute phases of solar dermatitis. After the acute symptoms subside protection against light is afforded by the use of an efficient screening ointment particularly one containing para aminobenzoic acid. Some patients respond satisfactorily to the internal administration of

tablets of para-aminobenzoic acid, each tablet containing 0.5 gm of the drug A total dosage of 8 to 10 gm. of the drug daily over a period of two or three weeks is sufficient to effect a cure in these patients.

In pellagra, vitamins B and C should be given in addition to nicotinic acid. Patients with bullous and erosive pigmented porphyria should not take fruit juices or fresh vegetables because of their content in chlorophyll. In other types of solar dermatitis the diet should contain ample quantities of vitamin and protein.

Indulgence in alcohol should be strictly forbidden in all patients with actinic or porphyric dermatoses. In addition to its neutralizing action on vitamins, alcohol usually adds further insult to a liver already damaged by its use over a long period of time.

The reported excellent results obtained in the United States and England with the synthetic antimalarial drugs in polymorphous light eruptions were not duplicated in my patients. During the past year I treated a number of patients having different forms of actinic dermatitis with these drugs. Some of them showed satisfactory improvement, others failed to respond. This is in agreement with the results obtained in Costa Rica and other tropical countries where the sun's rays are more intense and prolonged than in temperate zones

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Hot Climate Miliaria — Disease or Sign?

By
Frederick Sargent II, and Herbert Slutsky

South winds induce dullness of hearing, dimness of vision, heaviness of the head, torpor and languor: when these prevail such symptoms occur in diseases.

HIPPOCRATES

It is a curious observation that a study of the literature on the miliarias discloses that the majority of investigators have probed only skin-deep in their studies of these sweat gland dysfunctions. Some reviewers have either failed to mention that profound physiologic changes occur concurrently in the body as a whole or they have passed over such facts as curiosities. The impression created by this unholistic approach is that the miliarias are a group of diseases. On the contrary, the facts are that the miliarias are signs or indices of unacclimatization. In this discussion we shall consider the miliarias of hot dry or hot moist regions. When exposed to a nonspecific stress such as extreme heat, the body exhibits functional alterations which suggest deterioration of the state of acclimatization. Hot climate miliaria is a sign of this dysfunction.

Clinical studies undertaken by medical officers serving with the Armed Forces disclosed the significant fact that under appropriate environmental conditions up to 100 per cent of certain military units developed miliaria rubra. Among 35 to 70 per cent of these men, the miliarial lesions progressed to the point of producing a defect in their normal sweating mechanism. About one per cent of them became severely incapacitated as the result of more serious complications of miliaria rubra.

SYNOPSIS OF DERMATOLOGIC KNOWLEDGE OF MILIARIA

This dermatologic summary is based largely on the excellent reviews by Shelley and his associates. Miliaria rubra is only one of three recognized miliarial disorders which are caused by retention of sweat in a functional eccrine sweat gland. Miliarial lesions usually involve parts of the body covered with clothing Only rarely do they appear on the face and lower extremities and never on the palms and soles. Characteristically they are accentuated by agents which provoke sweating and diminished by agents which reduce sweating Depending upon the number of glands involved and the chronicity of the disorder various degrees of anhidrosis are produced.

The three types of miliarial lesions can be distinguished by clinical examination of the patient and by microscopic study of the skin. **Miliaria crystallina** is an asymptomatic eruption consisting of small, superficial, noninflammatory vesicles which persist but a short time. Both the vesicles and the sweat ducts contain sweat. Rupture occurs easily and sweat is poured out on the skin. Histologic sections show that the vesicles are located in the corneal layer Most of the sweat duct orifices are closed by keratin plugs, causing distention of the sweat ducts.

Miliaria profunda is not associated with any symptoms referable to the skin. It is a characteristic lesion in patients with tropical anhidrotic asthenia. The noninflammatory papules arise over the orifices of the sweat ducts, giving the skin a gooseflesh appearance. The vesicle in miliaria profunda is deeply situated and results from rupture of the duct below the level of the epidermal-dermal junction, whereby the sweat is dissipated in the adjoining tissue Since most of the sweat ducts participate in the process, anhidrosis results

According to Sulzberger and O'Brien, chronic maceration of the skin surface resulting from prolonged and excessive sweating brings about abnormal changes in the epidermis and leads to closure of the sweat duct pores. This closure and the symptoms associated with it have been identified as the sweat retention syndrome. These investigators postulate that the symptoms of the sweat retention syndrome are due to anhidrosis and the retention of sweat. In other words, this hypothesis attempts to

explain the symptoms of the sweat retention syndrome entirely in terms of local abnormalities in the skin. This hypothesis as the present discussion will bring out, neglects consideration of the organism as a whole

There are several significant *complications of the miliarias* particularly miliaria rubra tropical anhidrotic asthenia, tropical impetigo syringadenitis suppurativa tropicalis thermal asteatosis, and tropical dermatitis Concerning most of these conditions there is very little ecologic data. With the exception of tropical anhidrotic asthenia, these conditions will not be discussed further

ECOLOGY OF THE MILIARIAS

In considering *the natural history* of miliaria rubra, the three components of the interaction between organism and environment, i.e., environment, organism, and function, will be discussed.

The Environment. Three conditions of the environment play an important role in the etiology of miliaria rubra. They are the weather the clothing, and the occupation

Miliaria rubra occurs under two types of weather stress moist heat, which characterizes the tropical and subtropical zones, and dry heat, such as occurs in the deserts. According to Horne and Sams, the disease shows a distinct seasonal cycle, most cases occurring in the hot season. For hot moist regions, the significant meteorologic factor is a minimum temperature of 80° F or above Humidity also plays a role for coastal regions which are humid have a significantly higher incidence of miliaria rubra than inland areas which are drier and have lower minimum and higher maximum temperatures Under controlled conditions in *climatic chambers* miliaria rubra can be regularly produced in healthy young people continuously exposed to effective temperatures of 85 to 90 F for 24 hours Duffner showed that if the subjects spend only four to seven hours under these conditions and 17 to 20 hours at 75 to 78 F the incidence drops from 100 per cent to 10 per cent.

In the desert, on the other hand miliaria rubra does not appear in large numbers of subjects until the maximum temperature exceeds 110 to 115 F and the dew point 50 to 60 F Even then the incidence is lower than in moist hot regions according to Ladell, Waterlow and Hudson.

When the process of evaporative heat loss is taxed, the incidence and severity of miliaria rubra are increased. In hot, humid regions, this stress in correlated with a chronically wetted skin. In hot, dry climates, on the other hand, evaporation is so rapid that the skin is not chronically wetted. This fact casts doubt on chronic maceration of the skin surface as being the basic factor in the etiology of miliaria rubra. The load on the mechanism of evaporative heat loss would appear to be the more common causative agent. Clothing and occupation are factors which accentuate or moderate the effects of the ambient environment.

Under natural conditions, anywhere from one to seven months of exposure to hot weather must have taken place before miliaria rubra develops On the average, tropical anhidrotic asthenia, if it occurs at all, appears about eight weeks after the onset of miliaria rubra. However according to O'Brien, many cases with the former disease report for treatment suffering from both conditions concurrently

Most observers agree that while the intensity of heat may be the important element for the development of miliaria rubra, the duration of hot weather is the significant factor for the appearance of large numbers of cases of tropical anhidrotic asthenia. Ladell, Waterlow and Hudson, for example, report that most of their cases appeared at the end of the hot season.

Considerable field and laboratory investigations have been conducted on the role of ultraviolet radiation as a meteorologic element causing miliarial lesions. The results to date are conflicting and suggest that the effect of such irradiation is nowhere near as significant as temperature and humidity

The Organism. Here we deal with such factors as race, age, sex, habitus, and constitutional tendency Natives of hot, moist areas are less susceptible than immigrants. Negroes are no less prone to the eruption than other races. It may be that individuals older than thirty years are more susceptible to miliaria rubra than those younger Males and females are equally susceptible. The only aspects of habitus which have been critically investigated are complexion obesity and constitutional tendency but the differences are small and actually only suggestive.

The Function. The observations which we shall summarize at this time are based largely on the researches of two groups of

workers Ladell and his associates in Iraq and Nigeria and Horne and Mole in Karachi, India. In order to make the most concise summary of the various functional alterations which may occur in patients with various types of miliarial skin manifestations, we shall discuss an average patient. This patient will first develop miliaria rubra, then miliaria profunda, and finally tropical anhidrotic asthenia.

Our patient reports to the infirmary for treatment of prickly heat. The history reveals that he has been in the tropics for six months and that during this time he has been ingesting some 20 grams of sodium chloride daily When a physiologic study is made three deviations from the normal stand out there is reduced sweating from areas of skin free from the rash the sweat contains more sodium chloride than that collected from controls studied at the same time, tests in a climatic chamber demonstrate that this individual has lost his acclimatization to heat. We prescribe symptomatic treatment and request that the patient report back to the laboratory for periodic examinations.

Within a few weeks after subsidence of the acute episode of prickly heat, we notice that on the patient's skin there has appeared a new lesion which looks much like gooseflesh At this time the patient reports that sweating has become less over the trunk, but he has no local or systemic complaints. Further studies indicate that the rate of sweating has been reduced not only in the areas of miliaria profunda but also in areas free from the disorder On the face however the rate of sweating may be somewhat increased. The sweat chloride is higher than normal and somewhat less acid. The skin temperature is elevated about 1 C. above that of healthy controls

Two weeks later our patient is brought to the emergency ward in a serious condition He is breathing rapidly and deeply and is near collapse He is placed in an air-conditioned ward where he is considerably improved within a few hours According to his story he noticed during the preceding fortnight the gradual development of dizziness headache loss of appetite frequency of urination and progressive weakness. His skin felt hot and tense and he had a feeling of warmth He reported that the skin of the trunk and arms had stopped sweating, but that sweating had con

tinued on the face and forehead. These symptoms were exaggerated by work or exposure to the sun during the heat of the day and frequently at this time he experienced palpitations, breathlessness, and tingling of the hands and feet.

Examination of the patient discloses anhidrosis of the trunk and arms, miliaria profunda, a slightly elevated rectal temperature, and normal sweating on the face and forehead.

During convalescence from this episode, which takes somewhat more than one month, further physiologic studies are made. The rate of sweating from areas free of the miliarial lesion is reduced about 70 per cent. Intramuscular injection of atropine causes a greater reduction in sweating than that measured in healthy controls. The sweat chloride is elevated to more than twice that of healthy controls. This high concentration of sweat chloride persists as long as one month after complete clinical recovery. The patient is instructed to drink 1000 milliliters of water and his urine is collected during the following two hours. In contrast with normal subjects who excrete 98.5 per cent of the water in the two-hour period, our patient voids only 58 per cent. This abnormality persists for as long as six months after clinical recovery.

During the course of his hospitalization, study of the urine revealed that he was not retaining sodium normally. Normal retention could only be brought about by the administration of desoxycorticosterone acetate.

The facts suggest that patients with miliarial lesions and the clinical syndrome called tropical anhidrotic asthenia are suffering from reduced function of the adrenal gland. Furthermore, it is quite probable that cases with the clinical syndrome also have a mild form of tetany resulting from the rapid and deep ventilation which is characteristic of that condition. The physiologic and clinical observations which suggest reduced function of the adrenal gland are elevated sweat chloride, low recovery of water after the oral test, failure to retain sodium except when given desoxycorticosterone acetate, intolerance for heat, reduced sweating from clinically normal skin, and increased sensitivity to atropine.

On the basis of this study of miliarial conditions, we feel that the following several conclusions are justified.

1. Miliarial lesions are caused by pathologic changes in the

skin of persons exposed for long periods of time to environmental conditions which unduly tax the mechanism of evaporative heat loss

2. Chronic exposure of men to such ambient conditions, especially if the individuals are engaged in some degree of physical exertion, leads to a condition which we might call "dysacclimatization."

3. A vicious cycle develops in which miliarial lesions accentuate the deteriorating state of acclimatization Patients in this condition may develop *tropical anhidrotic asthenia.*

4. The evidence presented here lends strong support to the hypothesis of Ladell "that prickly heat is a precipitating factor leading to the breakdown of the already severely strained but hitherto adequate adaptation." It is evident then that miliarial conditions are but signs of a profound metabolic derangement rather than diseases per se.

5 The therapeutic implications of these theoretical conclusions are that patients with miliarial syndromes should be placed in an environment which reduces the load on the mechanism of evaporative heat loss and severe cases, especially those with tropical anhidrotic asthenia, may require supportive treatment with adrenocortical hormones

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The Deficiency (Nutritional) Dermatoses

By
Frederick R. Schmidt

BIOCHEMICAL oxidation can not function in the presence of defective catalytic energy systems These systems are normally composed of enzymes, vitamins, proteins, and minerals. A defect may be due to a shortage of one or more of these elements, inability of the host tissues to utilize them or partial want of oxygen.

The factor of vitamin deficiency is universally regarded as the cause of certain disorders associated with cutaneous symptoms. Hippocrates, for example treated syndromes associated with night blindness with a diet rich in liver thus anticipating by some 2500 years the current belief that hepatic dysfunction is concerned in the production of this condition.

The problem is complicated by the circumstance that many of these dermatoses are caused by multiple vitamin deficiency Pellagra, for instance is not only caused by relative want of nicotinic acid but also by a shortage of other fractions of the vitamin B complex. The complexity of the problem as well as the difficulty encountered in disassociating the vitamins from each other as activators in the complicated energy systems of enzymes vitamins, and proteins has been repeatedly stressed.

The clinical pictures of phrynoderma and cheilosis produced by vitamin A and riboflavin deficiencies respectively are well known. On the other hand it is suggested by some investigators that it is not the deficiency of vitamin A but the inability to utilize it which causes keratosis follicularis and acrodynia.

Beriberi, a disease found in persons with faulty eating habits including chronic alcoholics and drug addicts is not only due to

thiamine and other vitamin deficiencies but also to a shortage of or an inability to utilize magnesium and phosphates

Thus the problem grows more difficult. With the knowledge that relative want of thiamine is concerned in the production of beriberi, we may look a little further into the mode of action of this vitamin. Thiamine in its active form of thiamine pyrophosphate is identical with cocarboxylase, a coenzyme for pyruvate oxidase. In the breakdown of glycogen to lactic acid, pyruvic acid is an intermediate metabolite which requires cocarboxylase and pyruvate oxidase to complete its degradation to lactic acid. Thus the failure to metabolize pyruvic acid leads to interference with cellular respiration and melanogenesis. We learn from this that not only the energy system of enzymes, coenzymes, vitamins, and minerals is concerned in beriberi but also carbohydrate metabolism and biochemical oxidations.

Thiamine also potentiates the action of acetylcholine, the vasodilator hormone of the body by neutralizing cholinesterase.

Vitamins are also important items in the nutritional requirements of a number of dermatophytes. This was recently demonstrated by Sullivan, Bereston, and Wood, in showing that thi amine deficiency exists in Trichophyton tonsurans.

Sprue is of interest to the dermatologist because of involvement of the tongue and skin. The tongue at first appears inflamed with tiny whitish vesicles occurring in crops. Later it becomes thickened, and atrophy of both the filiform and fungiform papillae sets in. The skin is dry and wrinkled and occasionally hyperpig mented. In patients observed in Puerto Rico the frequent occurrence of perleche was noteworthy The similar appearance of the tongue in sprue and pernicious anemia suggests treatment with folic acid or folinic acid in the form of calcium leucovorin and cyanacobalamine (vitamin B_{12}) while the presence of per leche indicates the need for riboflavin. The daily dose of folinic acid administered orally is 15 mg.

The improvement noted by Corrales and me in patients with polymorphous light eruptions and in those with actinic spotted achromias following the administration of thiamine and nicotinic acid may be attributed to the activation of the enzyme systems concerned in cellular respiration and the formation of pigment.

Bonilla recently introduced the use of vitamin D_2 (calciferol) in the treatment of chromoblastomycosis. His preliminary report of favorable results is summarized in the section dealing with chromoblastomycosis.

Pregnant women with varicose veins when given vitamin E, usually notice improvement in the condition of the veins. Associated itching and pain may be greatly relieved. Since these women are also more apt to have a normal pregnancy when given vitamin E, it is possible that the betterment in the condition of their veins and circulation is connected in some way with the actions of both vitamin E and the adrenal steroids.

Vitamin E, in my experience, has not proved effective in chronic discoid lupus erythematosus probably due to the low dosage used. Neither have I been impressed with the reported favorable action of vitamin P in controlling capillary bleeding or of vitamin K in the management of hemorrhage associated with decrease in plasma prothrombin.

Seborrheic dermatitis is a disorder which is frequently confused with "atopic dermatitis," especially when it occurs on the back of the neck, the forehead, eyelids and about the mouth. In taking histories of seborrheic dermatitis I have noted the frequency with which persons with this disorder state that they were breast fed as infants for at least several months. It is common knowledge that babies with the disorder frequently recover when they are removed from the breast. This has been attributed to the fact that pyridoxine which is associated with casein is more abundant in bovine than in human milk. When I first published this observation, I was giving these people pyridoxine by mouth with the idea that seborrheic dermatitis is a symptom of pyridoxine deprivation. This form of treatment proved ineffective.

Some years later Schreiner and his associates confirmed my observation on the ineffectiveness of oral pyridoxine in seborrheic dermatitis. They found, however that when rubbed into the lesions in ointment form (10 mg per Gm.) the vitamin effected clearing in 5 to 21 days Unfortunately the lesions usually recurred after the use of the ointment was stopped, an experience which I share with these authors. The studies carried on by Schreiner and his associates are interesting in that they present a concept of disease due to a local metabolic defect.

The importance of vitamin C in the maintenance of normal connective tissue was pointed out by Danielli and his coworkers They showed that collagen is not formed in the absence of vitamin C.

The evidence obtained from recent experiments indicates that a reciprocal action exists between vitamins and minerals and that the effectiveness of a vitamin is greatly increased by giving it in combination with its specific activating mineral or minerals.

This is particularly true of the minerals present in minute quantities. There is a good deal of talk about these trace minerals, the discussions usually revolving on whether or not the occurrence of a deficiency of these elements in man may be attributed to a lack of them in the soil. In the United States this does not seem possible in view of statistics showing that even a diet of mediocre quality easily supplies the daily requirements of copper cobalt, zinc, magnesium, manganese, and other trace minerals However there is an increasing bulk of evidence to the contrary what with the effects of soil erosion, lack of rotation of crops, improper and faulty fertilization, and other factors. The world supply of the precious six inches of top soil is shrinking at a terrifying rate.

This is taking place at an accelerated rate in the southern parts of the United States, Mexico, Central America, and most of South America. The relatively small amount of minerals consumed by most persons living in these areas can not properly catalyze the vital enzyme systems or activate vitamins. The soil is greatly depleted, and rotation of crops is not practiced. This causes nutritional and nervous disorders characterized by anemia and demyelinization.

Solutions of cyanacobalamine owe their purplish tint to the presence of cobalt. The profound stimulating effect of this cobalt containing vitamin on erythropoiesis is of interest to dermatologists in the treatment of ulcers associated with sickle cell anemia. Wolf and Levy recommend giving patients with this disease 12 cc. of a 2.5 per cent aqueous solution of cobalt chloride divided into three doses for a period of three weeks. Ferrous sulfate in doses of 1.8 Gm. daily should then be given together with the cobalt for two more weeks. The improvement noted in 75 per cent of their patients was dramatic.

Copper is another trace element which, although present in minute quantities in food and the body acts essentially as an enzyme. Since the daily intake of 2 mg of copper will maintain adults in balance and this amount is easily covered by the average diet in the United States, it becomes evident that any benefit derived from replacement therapy of a missing trace mineral like copper is due to the action of that element as an enzyme

Two examples of the enzymatic action of copper will suffice for the purpose of this discussion A slight relative want of copper greatly reduces cutaneous cytochrome oxidase. It will be recalled that this enzyme activates molecular oxygen and accepts electrons from cytochrome, resulting in profound interference in the oxidative processes of the skin

In the biochemical oxidations associated with the formation of melanin in the skin, Lerner and his associates recently showed that the amino acid tyrosine is converted to melanin by the copper-containing enzyme tyrosinase which is found in the cytoplasm of melanocytes It will be recalled that sunlight oxidizes the sulfhydryl groups inhibiting the catalytic system of enzymes partly concerned with the melanin formation

Each one of the remaining trace minerals apparently acts essentially as an enzyme Zinc for example is normally found in all cells where it regulates the synthesis of carbonic acid, a metabolite of importance to individuals living at high altitudes by controlling the potassium chloride ions and carbonic anhydrase concerned in its formation. Potassium chloride ions with magnesium and phosphate ions are considered essential to effective oxidation.

The relative want of magnesium ions found by Engman in patients with neurodermatitis may help to explain disturbances in the biochemical oxidations associated with this disorder

Low blood phosphate levels were encountered in two patients with chromoblastomycosis following prolonged treatment with calciferol. Normal levels were reestablished when the administration of calciferol was stopped for six weeks

Manganese is important in preventing the tremendous yearly loss of fertilizers on farms in the United States It neutralizes the enzyme that destroys the potency of sulfur lime potassium and nitrogen, and its absence in milk obtained from cows grazing on

land lacking in manganese is looked upon by some biochemists as a factor in the production of human brucellosis.

The quantitative spectrographic analysis of blood from patients with skin lesions occasionally reveals abnormalities in the mineral content. This was first made evident to me in a patient with lymphatic leukemia, in whom a nonspecific papular eruption occurred. The spectrogram showed a high degree of zinc depletion. On the other hand, in a patient with advanced lesions of mycosis fungoides, no appreciable fluctuations from the normal mineral content were found, suggesting a different pathogenesis in this disorder from that in leukemia.

Knowledge concerning the effect of essential amino acid deficiency in cutaneous disorders has recently gained impetus through the use of isotopes. This technic showed that the glycine molecule goes to make up creatine which is concerned with oxidative processes in dermatomyositis.

Scott recently produced experimental proof of the importance of histidine in the normal growth of rats. His studies showed that rats placed on a purified diet completely deficient in histidine developed regressive tissue changes in several organs in which the tissue completely recovered its normal structure when the histidine was added to the diet.

The results with oral methionine in four patients with psoriasis, showing high blood cholesterol levels were unimpressive. That this amino acid is concerned with cholesterol metabolism, however was brought home to me recently by the improvement in more than 20 persons with psoriasis following treatment with massive doses of vitamin B_{12}. It will be recalled that the pharmacologic effects of this vitamin include both a lipotropic action and a methionine sparing effect resulting from direct participation in the synthesis of methionine. The details of this treatment are given in the section on psoriasis.

Deficiency of dietary fatty acids such as linoleic or arachidonic acid occasionally provokes a disorder characterized by dryness and cracking of the skin, especially of the ears hand, and eyebrows.

Kwashiorkor or multiple-deficiency syndrome occurs almost exclusively in very young children. It is due chiefly to protein

malnutrition the associated deficiency of amino acids and vitamins being of secondary importance Among the skin changes noted in Costa Rica are depigmentation, dusky purple patches which do not blanch, edema, linear fissures in various areas of the body and a dry "crackled or "mosaic" skin A striking feature is the "flag sign" which consists of bands of very pale-colored hair seen best when the strands of hair are held up against the light.

TREATMENT

A diet high in protein and vitamins and low in fat and carbohydrate is essential to the well-being of persons with true deficiency (nutritional) disorders. It should be remembered in this connection that prepared foods sometimes lose 100 per cent of their vitamins, while milk loses vitamins by standing in the light as well as by heating.

The particular vitamin required for the treatment of a deficiency disorder with few exceptions is best given by mouth Combinations of vitamins often exert a stronger action than when given singly as for example blood vitamin C levels are raised when riboflavin is added to vitamin C.

The action of both vitamins and enzymes is enhanced by combining them with their specific activating or catalyzing trace minerals. Copper should therefore be combined with ascorbic acid and folic acid. Cobalt, manganese and zinc, as previously mentioned, are also catalyzing agents.

Calcium when used as replacement therapy in deficiency diseases of the skin, should only be given by mouth. Given intravenously it is not well ionized and acts solely as a vasodilator Three or four teaspoonfuls daily of calcium gluconate provide sufficient calcium for ionization by the gastric hydrochloride acid. In some instances this process is aided by the addition of vitamin D to calcium gluconate. Iron or iodine are often desirable minerals to give together with calcium.

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The Exanthematic Rickettsial Fevers

By
Frederick R. Schmidt

RICKETTSIAE occupy an intermediate position between viruses and bacteria, resembling the former in that they grow only in the cytoplasm and nuclei of living cells and the latter because they appear as cocco-bacillary forms. The common reservoir of rickettsiae includes ticks or garrapatas and the small domestic and wild rodents on which they feed, the organism being carried to man and other mammals by ticks, fleas, and lice. Ticks are congenitally infested with rickettsiae and introduce the organism into a victim with the saliva of the bite or by contamination with the feces

Since ticks are infested with rickettsiae a high incidence of tick-borne rickettsial fevers might be expected in regions inhabited by large numbers and varieties of these acarids This expectation is realized in the western parts of the United States, where
Rocky Mountain fever is frequently encountererd. On
the other hand, r fevers rarely oc Central America
and the islands t Indies, regio nding in great
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spotted fevers, especially of the Mexican type of murine typhus fever with yellow fever is possible only in sporadic instances of the disease.

There are several distinct groups of rickettsial fevers of which classic exanthematic typhus fever or tabardillo heads the most malignant group. It is caused by Rickettsia prowazeki, variety prowazeki, and is transmitted from man to man by the body louse The characteristic rash first makes its appearance on the trunk and in the axillae, usually between the fourth and seventh days of the disease, spreading rapidly over the entire body with the exception of the face, palms, and soles. The early lesions are pinkish or bright red macules and maculopapules which light pressure causes to fade completely Petechial elements soon overshadow the initial lesions, their number and intensity depending on the severity of the process. The rash may not appear in persons previously receiving antityphus vaccine, and if it does, it is usually of short duration.

Snyder regards **Brill's disease** or **sporadic typhus** as a flare-up of classic louse-borne typhus fever cropping up years after the primary infection, its occurrence in the Americas being noted chiefly in immigrants from European areas where classic typhus is wont to occur The rash is absent in many patients, the course of the infection milder and the prognosis as to life better than in classic louse-borne typhus.

The similarity of the rash in Brill's disease and **endemic murine typhus fever** occurring especially in Mexico and the southeastern part of the United States arouses suspicion that the two disorders are one and the same. Although the outcome of the agglutination and complement-fixation tests made with the sera of patients with these diseases indicates their close relationship to each other and permits their placement in the same group with classic typhus, it is necessary for purposes of control measures to distinguish between them.

The reason for this necessity is that the transmitting agent is usually different in the two disorders. The vector in most instances of Brill's disease is the human body louse and in the majority of cases of murine typhus fever the rat flea X. cheopis. The rat flea becomes infected with rickettsiae from feeding on a

rat which has been freshly infected with Rickettsia mooseri, the etiologic agent of murine typhus

The difficulty of instituting proper control measures against the animal reservoir and the transmitting agent is increased by the circumstance that the human body louse occasionally replaces the rat flea in carrying the infection from man to man. This may account for the confusion existing in Mexico some years ago between classic louse-borne typhus and murine flea borne typhus.

The rash in murine typhus usually appears on the fourth or fifth day and is composed of pinkish macules and maculopapules that first arise on the trunk and then spread rapidly over the entire body with the exception of the face, palms, and soles. A certain similarity exists between the rash in murine typhus and that in rat bite fever

The existence of cross-immunity has been demonstrated between classic typhus, Brill's disease, and murine typhus About the sixth day of the infection agglutinins usually appear in the patient's serum which may be tested against Proteus OX 19 by means of the Weil Felix reaction A positive Weil-Felix test indicates the presence of infection, especially when successive tests show increasing titers. A negative response, however does not exclude the existence of infection, because neutralizing antibodies may not appear in the blood until relatively late in the course of the disease.

The difficulties encountered in obtaining an optimal antigen density for general use in determining the mean titers of sera in the Weil-Felix test were recently stressed by Schubert, Holdeman, and Martin. They also emphasize the need for standard ization of materials and methods used for the routine serologic diagnosis of rickettsial diseases.

The second group of rickettsial fevers associated with a rash is the Rocky Mountain spotted-fever group These disorders are variously known as Lone Star tick fever Tobia, and Sao Paulo fever Colorado tick fever however in spite of having a common transmitting agent, is not a member of this group being caused by a virus and characterized by the absence of a rash. Rocky Mountain spotted fever as it occurs in the United States, is caused by Rickettsia rickettsii and carried from rodents to man

by various ticks, the most common of which is Dermacentor andersoni.

The onset of the disease in persons who have not been vaccinated is sudden, with fever headache, and many other aches. The rash consists at first of macules and papules of a violet red color which is soon superseded by petechial elements as in classic typhus fever The site of onset of the eruption and its subsequent evolution, however differ in the two disorders Whereas in typhus fever the process is met with first in the axillae and on the trunk, from which it progresses to the extremities in a centrifugal manner in Rocky Mountain spotted fever it shows first on the wrists and ankles and then spreads in a centripetal fashion to the legs, arms, and chest. The skin is exquisitely tender Gangrene and sloughing of the skin of the fingers, toes and buttocks generally occurs in patients succumbing to the disease.

A clinical distinction between various forms of spotted fevers, as they occur in different countries and under separate names, is not possible. The eruption associated with Sao Paulo fever for example, may sometimes consist of polymorphous elements, and at other times it may adhere closely to the recognized pattern of macules and papules that we associate with Rocky Mountain spotted fever This difficulty of differentiation is further enhanced in certain countries like Columbia, where Sao Paulo fever classic typhus fever murine typhus fever and rat bite fever occur concomitantly I recall seeing a spotted fever patient in Bolivia, in whom Veintemillas had great difficulty in distinguishing clinically between classic typhus, murine typhus, and a spotted fever

The diagnosis of Rocky Mountain spotted fever is, as a rule, not difficult in patients living in regions known to be infested with ticks, and in which the affection appears either sporadically or endemically A disease of uncommon occurrence, with which it may be confused, is toxoplasmosis.

The complement-fixation test is more sensitive than the agglutination test in detecting antibodies in Rocky Mountain spotted fever

There are two epidemiologically different rickettsial disorders that merit a brief consideration, tsutsugamushi fever or scrub

typhus and rickettsialpox. The first of these diseases is not native to the Americas, but it may appear here as a result of importation by the Armed Forces returning from the Orient. It is a chigger borne rickettsiosis, in which the primary lesion makes its appearance on the fifth day as a hard papule or eschar It occurs chiefly in the axilla and around the waist. The vesicle which forms on the eschar soon ulcerates and becomes covered with a black crust. This is followed by the appearance on the trunk of red macules and maculopapules on an inflamed skin, often spreading to the arms and legs. The rash usually persists for several days before disappearing

Rickettsialpox shows itself at the site of a mite bite as a red papule that soon becomes vesiculated, ultimately drying to form a black necrotic core. Similar initial lesions appear chiefly on the covered parts of the body the lesions at certain stages of the disorder all becoming vesiculated at the same time, a circumstance separating rickettsialpox from chicken pox. Greenberg and his coworkers demonstrated that mice serve as a reservoir of the causative organism Rickettsia akari. In rickettsialpox, there is a positive specific agglutination reaction, this being the only one of the rickettsial fevers in which patients fail to produce agglutinins for Proteus strains throughout the course of the disease. Complement may be specifically fixed at certain stages of the affection, but there is always some crossing with Rocky Mountain spotted fever

Q fever is only occasionally associated with a rash. The etiologic agent is Rickettsia burneti which in the United States is carried to humans chiefly by the wood tick, Dermacentor andersoni, or by contamination with its feces. A rash consisting of small pink macules, varying in number from a few to many appears on the chest, abdomen, and back in a very limited number of cases the lesions paling on pressure. The disease is more widespread than is generally believed. The diagnosis is made by the isolation of R. burneti or by the positive outcome of the complement fixation test.

Popularly known as shank fever because of the severe pains in the legs, trench fever is caused by Rickettsia quintana and is carried to man by the human body louse. The rash occasionally

accompanying the disease is composed of pale pink, evanescent macules and maculopapules on the chest, abdomen, and back.

Histologic sections of material taken from patients succumbing to classic typhus fever show severe inflammatory changes in the arterioles and capillaries of the skin. Rickettsiae can be demonstrated in the endothelial cells lining the small cutaneous vessels. The cells infected with rickettsiae become swollen, proliferative, and thrombotic as a result of rickettsial growth, and the perivascular infiltrate consists of polymorphonuclear leukocytes, histiocytes, and lymphoid cells

The tissue changes in the Rocky Mountain spotted-fever group and scrub typhus, although less severe, closely resemble those in classic typhus. It becomes evident from a careful study of the material taken from the brain, kidneys, subcutaneous tissues, muscles, and skin of patients succumbing to rickettsial fever that the blood vessels of these organs are the site of the principal pathologic changes in the early stages of the disease. They are the point of attack. The tissue alterations in these organs of the peripheral system are those associated with focal inflammatory reactions of the vessel wall, necrobiosis, and perivascular infiltrates of blood cells, histiocytes, and plasma cells.

The treatment of choice of the rickettsial fevers is with aureomycin, chloramphenicol, or terramycin. The combined use of para-aminobenzoic acid and an antibiotic in the treatment of the Rocky Mountain spotted fever group has proved of considerable value, for it is believed that para-aminobenzoic acid lessens rickettsial activity

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Bartonellosis

By
Frederick R. Schmidt

The initial hemic phase of the disease is characterized by constitutional symptoms of great severity If the patient survives, this phase is followed by the eruptive phase called verruga peruana.

The eruption usually appears toward the end of the hemic phase, although occasionally it is present throughout the entire course of the disease. The cutaneous lesions consist of papules and nodules, the latter occurring both in and under the skin. The primary element of the papillary type of verruga, according to Pedro Weiss is either petechial, vesicular or miliary papular resembling the pinhead-sized, transparent elevations of miliaria crystallina. A tiny crust usually covers the lesions masking to some extent their color which ranges from yellowish-red to bright red They are most constantly met with on the extensor surfaces of the legs, where they may be few or numerous discrete or coalescent. Occasionally they appear on the mucosa of the mouth and nose as the first elements of the eruption.

The histologic changes in the hemic phase of the disease, although rarely observed, consist at first chiefly of hemorrhage and thrombosis of the blood vessels and as the infection persists, proliferation of the granulation tissue. The causative agent, Bartonella bacilliformis, can be demonstrated in the swollen endothelial cells of the smaller arterioles and capillaries of the skin in patients with Oroya fever who show no sign of an eruption.

In the eruptive phase, parasites are present in the endothelium of the smaller blood vessels, although in fewer numbers than in

the hemic phase, and in small groups around the vessels some of them in perithelial cells and others lying free in the dermis. The newly formed capillaries anastomize freely in the dermis crossing each other in all directions but their lining endothelium is composed of only one layer of cells in contrast with the multiple layers found in malignant hemangio-endothelioma. The absence of mitotic figures further distinguishes a verruga from the latter disorder

Bartonella is cytophilic. It invades the red blood cells in the hemic phase, in which it assumes a thin bacillary shape from 2 to 3 microns in length, while in the eruptive phase, it has such various forms as coccoid, bacillary and amorphic granular masses. The organism is gram negative and colors readily with Giemsa's stain.

The nodules of the eruptive phase may be confused with multiple idiopathic hemorrhagic sarcoma, hemangio-endothelioma or hemangio-pericytoma, multiple angiomas, and pyogenic granuloma.

The prevention of the disease by such measures as insect spraying with DDT and leaving endemic areas before sundown have materially reduced its incidence. Persons having to live in these areas should sleep under a wire screen with a mesh of not less than 22 holes to the linear inch in order to keep out the sandfly.

The treatment in the hemic phase is purely supportive. The profound anemia encountered in these patients is a source of alarm to the uninitiated. Blood transfusions are not necessary because regeneration of red blood cells is rapid at the end of the febrile period. The use of the antibiotic drugs in relatively small doses destroys the parasites contained within the perithelial cells or on those lying free in the dermis.

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Skin Diseases Caused by Arthropods

By

Frederick R. Schmidt

Arachnidism. Lactrodectus mactans is the chief member of the black widow group of spiders responsible for most cases occurring from the southern part of the United States to Chile. The sting mark is a minute flat, purplish spot with a white *areola that either rapidly disappears or becomes red and swollen.* If venenation takes place on an extremity the skin distal to the bite sometimes acquires a marblelike appearance and gangrene ensues, the resulting ulcer healing with an irregularly shaped and ugly scar

Rosenberg, working in the clinic of Luis Prunes in Chile, showed that the marblelike appearance of the skin is due to arteriolar spasm induced by the action of the necrotic factor contained in the venom. He was able to prove this by the prompt administration of large doses of oral nicotinic acid and by the application of diathermy to the poisoned area, five to 10 treatments of 20 to 30 minutes each usually proving effective.

Intravenous injections of another type of vasodilator calcium gluconate, are often the only medication required in mild cases not showing marbelizing of the skin.

Allen recently reported success in treating a patient who had been severely bitten by a black widow spider with a preparation of curare called tubocurarine (Abbott) The dose used was 9 mg given very slowly intravenously Curare acts by inter posing a block between the muscle and the afferent nerve ending receiving the vasospastic stimulus released at the site of the bite.

Scorpions. Scorpion venom acts like spider venom, stimulat ing the sympathetic nervous system to discharge epinephrine into

the blood stream, thus producing vasospasm. The sting may cause death by paralyzing the cardiac and respiratory centers this being especially true in children in whom the ratio of the quantity of venom to the size of the child is far greater than in adults.

A suggested first aid management of scorpion poisoning is to place a piece of ice as soon as possible against the area of the sting Ice is then crushed and placed in water using more ice than water the effected part being put into this mixture for two hours. Whenever this is impractical, cold packs should be applied.

Acarids. Mites feed on plants and are found in practically every habitat available to animal life. Requiring a moist environment, in dry weather they will often attack man in their quest for moisture They frequently live as commensals of certain bloodsucking beetles flies and mosquitoes on which they cling to the abdomen long enough to deposit their eggs and larvae, which then find their way into man or other mammal at the time the insect bites and sucks blood. Other species are freeliving and predaceous.

Mites produce dermatitis by invading the skin, by brushing against it, and by feeding on the blood of the host. The human itch mite is an example of the first type, the onion mite of the second, and any of the pathogenic ticks of the third or bloodsucking type.

The ability of mites to transmit systemic diseases overshadows their role as etiologic agents in the production of cutaneous disease. Ticks carry many of the rickettsial fevers to man, and Dermanyssus gallinae is a vector of eastern equine encephalomyelitis virus.

Mite-caused dermatoses are frequent in persons working with mite-infested materials and therefore in these instances should be regarded as occupational dermatoses. The mildness of the average mite-caused dermatitis accounts for the paucity of cases seen by physicians.

Thousands of species have never been studied. The brightly colored Hydracarines, for instance, feed on water animals, crustacea, and insect larvae and like schistosomes probably cause

some instances of swimmers itch that occur so often on the beaches of Cuba, Florida, and Uruguay

Rat mite dermatitis. This disorder is caused by a Megisthanic mite the lesions consisting of vesicles, wheals urticovesicles, and papules usually showing a tendency to group in one area, commonly around the ankle where scratching often leads to infection.

Fowl mite dermatitis. Caused by *Dermanyssus gallinae*, this condition produces serious pests in chickens and pigeons and is carried to man either directly or by an intermediary host such as the starling It is met with on the neck, extremities, and around the waist, either as an itching urticopapular eruption or as erythema infectiosum. Persons cleaning out hen houses are liable to develop pustular dermatitis where the mite has irritated the skin, and scratching leads to infection.

Rickettsialpox. This disease is caused by *Rickettsia akari*, which is transmitted by a member of the Dermanyssid mites, the mouse mite.

Trombidiid mites. These and related species of mites cause a large variety of itching eruptions characterized by minute papules, papulovesicles pustules and urticarial wheals Among popular names for the eruptions are straw grain, copra, grocer's, baker's, mattress and water itch.

Pyemontes ventricosus. This mite lives chiefly as an ectoparasite on the larvae of the grain moth and the wheat jointworm and also infests wheat and barley grain, straw seeds vegetables, and plants. Workers handling grain or cutting and baling straw are liable to become infested as well as those working in flour mills or sleeping on infested mattresses. Infested straw used for bedding or in making strawboard is a common source of infestation. The eruption is accompanied by intense itching Secondary infection sometimes complicates a condition that is nothing more than a passing annoyance, since the mites remain but a short time on the skin and do not have time to do much damage.

Liliaceous bulbs such as tulip, onion, and garlic often become infested with brilliantly colored Trombidiid mites Men handling these bulbs may develop a rash consisting of papules soon becoming excoriated and covered with a crust, to the accompaniment of intense itching The symptoms are produced by the mite and

its excretions coming in contact with the skin. Similar mites also cause cheese and fig mite dermatitis as well as vanillism, the latter condition being met with in handlers of vanilla pods.

The prophylactic use of the newer insect repellents was found effective by Booth and Jones. They recommend diluting the repellents with water and impregnating the clothing. The early use of soap and water and a change of clothing followed by the application of a shake lotion is effective treatment in my experience.

Demodex folliculorum This is the follicle mite which occasionally produces the picture of rosacea. It also causes diffuse pigmentations of the face in women who habitually clean their faces with creams instead of soap and water a condition that should not be confused with pigmentation due to the use of Vaseline. Agglomerations of these parasites in the meibomian glands occasionally induce dermatitis about the eyes.

Trombidiosis. This is caused by the species of Trombiculid mites known as chiggers or red bugs in the United States and as bichos colorados or usapucas in Argentina. Infestation with chigger larvae should be distinguished from dermatophiliasis that is caused by the chigoe flea. Chigger larvae parasitize terrestrial vertebrates including man, particularly after heavy rains in summer The bite is usually not felt, but itching sets in at once, directing the attention of the victim to the sting mark, which is a red spot soon becoming a papule with a central red dot.

Ticks or garrapatas. These mites belong to the order of Ixodides and are the best known mites, probably because they are large enough to be visible to the naked eye. A few species, like the Mexican tlalaja, are venomous. Practically all ticks are parasitized with rickettsiae living and multiplying in the nuclei of the parasite s cells, the rickettsiae apparently being transmitted hereditarily and passed on to man in the saliva of the bite. In addition to serving as intermediary hosts for rickettsiae ticks of the genus Ornithodorus are vectors of Borrelia recurrentis and certain bacteria.

One might conjecture from this that tick borne fevers are of frequent occurrence in areas abounding in ticks. This is spe-

ently not so however because the incidence of these disorders in regions densely populated by ticks is often very low In Cuba, for example, Pardo-Castello found only a few reports of what he considered doubtful cases and in Central America I did not encounter a single instance of rickettsial fever

Spinose ear tick. This is a member of the Argasid family and occasionally invades the external ear canal, where it produces a very painful bite. Complications of a serious nature may set in.

Dermacentor andersoni or wood tick. This tick penetrates the skin without being noticed by the victim in whom it provokes a hard papule. This and the dog tick are responsible for occasional cases of allergic reactions and even paralysis besides being the vectors of the causative agents of tularemia and Rocky Mountain spotted fever The Lone Star tick transmits spotted fever in Texas and Oklahoma. A closely related tick, Ixode ricinus derives its name from the circumstance that the fully engorged female looks like the seed of a castor oil plant. It sometimes gets under the nail, forming a small tumor

An unusual manifestation of tick bites observed in Central America is a red macule that grows in size rather rapidly within a few days to cover a large portion of the body A sensation of burning is intense The lesion disappears by leaving a brown pigmentation, the picture somewhat resembling erythema chronicum migrans.

A few applications of liquid collodion or kerosene to the sting mark made by a tick is generally sufficient to suffocate the animal. A combination of DDT with pyrethrins or nicotine has proved effective in tick control.

Scabies or sarna. This disease results from infestation with species of the genus *Sarcoptes* the genus *Psoroptes* being responsible for sheep goat, horse, and cattle scab Mites of animal origin are easily carried to man, dogs donating parasites to their masters in whom they commonly produce reddish macules and papules confined to the areas of contact and only infrequently urticarial papules similar to those of papular urticaria.

Three peculiarities of infestation with mites of animal origin serve to separate them from those due to the human mite. They are first, that the victim starts to itch on the day he comes in

contact with the animal, second, that there are very few if any burrows and third, that the mites leave their host when the animal contact is removed.

In human scabies, on the other hand, itching does not set in for a week or more following infestation, and the sarcoptid, in contrast with the Psoroptic mite, burrows into the skin. Borda demonstrated that it requires generally from 15 to 20 days for the clinical signs of the disease to make their appearance. By this time the patient has become hypersensitive, so that the majority of the symptoms are the result of an altered state of reactivity of the host to the acarus This conclusion, however does not exclude the possibility of an occasional case of scabies of animal origin lasting for a long time, as in persons being repeatedly reinfested by their dog s mange.

Norwegian scabies. Characteristic of this disorder are the hyperkeratotic crusts of a dirty gray color piled up in irregular masses in the areas of predilection of scabies. At times the whole body is covered with scales resembling generalized neurodermatitis with hordes of mites swarming under the crusts. Atypical and extremely variable forms of the disorder often pose a difficult problem in diagnosis.

Cachectic individuals fall an easy prey to its ravages. This is attributed by many to a lowered resistance brought on by a deficiency or lack of dietary vitamins. One might wonder whether the weakened condition of the patient is the cause or effect of the tremendous infestation.

During a visit to Chile, I observed a good many patients with Norwegian scabies. Is it possible that the original scabietic infestation had run wild over their emaciated bodies, not because they were not getting enough vitamins, but because they were unable to buy soap? At that time soap was too expensive for many Chileans, as in Central America, where the incidence of scabies rises sharply during the rainy season, when the washing cannot be hung out in the sun, and the native population to a great extent uses wood ash or the pulp of a native fruit in lieu of soap.

Patients should be instructed in the proper application of a preparation containing benzyl benzoate or sulfur for although

proprietary preparations such as Kwell and Eurax are more efficient and less messy they are unavailable in many parts of Latin America.

INSECTS

The great majority of insect bites in the temperate zone are of a benign character In the tropics, however swarms of insects not only inflict vicious bites but also act as intermediary hosts and transmitters of serious disease Phlebotomus for example, serving as the intermediary host for *Leishmania tropica* and *braziliensis* and Triatoma, which is the etiologic agent of Chagas disease.

It is often difficult to decide whether the presenting lesions are due to the bite or to toxins elaborated by the insect in some distant focus presumptive evidence in favor of one or the other being frequently the deciding factor Various factors that may decide the question are the localization and character of the lesions taken in conjunction with the time of their appearance following a history of a known bite.

Another example of this difficulty is the occurrence of papular urticaria and erythema multiformelike bullous eruptions associated with flea bites. Here we have to rely on the same clinical criteria to differentiate between what is hypersensitivity and what is the direct effect of the bite

The method of transmission of pathogenic micro-organisms by insects has been the subject of considerable research. Insects apparently convey parasites to a definitive host chiefly by fecal material and to a lesser degree by their probosci, feet, and body hairs. Vanni demonstrated that the fecal material of flies contains trypanosomes amebae and other protozoa living in the posterior gut of the fly while bacteria are found in the material regurgitated from the esophagus and anterior intestine, a drop of this yellowish fluid being spit up by the fly and deposited in its flight.

Many insects are venomous The nature of venom and its mode of action are subject to speculation. Persons experiencing systemic reactions to bee stings are also hypersensitive to bee, wasp and yellow jacket stings, having been sensitized by previous stings. It has been suggested that this excessive sensitivity is

due either to protein in the stinger or body of the bee or to histamine contained in the venom. In either instance, vascular reactions are set in motion.

It is advisable to try to desensitize persons who have had at least a moderately severe sting of this kind, because subsequent stings are liable to induce reactions of greater intensity or even death. Mueller and Hill recommend using "a mixed extract of bee, paper wasp and yellow jacket, first doing an intracutaneous test with a 1 1,000 000 dilution of this material. If the test is negative, treatment should be started with 0 1 cc. of this dilution and continued at weekly intervals, gradually increasing the concentration until a dilution of 1 10 is reached, using 0.3 cc. of this dilution, these authors recommend continuing with this dosage unless the patient proves too sensitive.

Centipedes and millipeds. Several species of these insects are venomous, producing rather severe systemic reactions. The milliped occasionally causes vesicular dermatitis.

Caterpillars or gusanos. These long wormlike larvae of butterflies, moths, and other insects are great pests in the tropics. The word gusano" is generally employed by the people of Latin America to mean both caterpillar and larva. Thus there are two kinds of gusanos, the caterpillar with hairs and the tiny white, wriggling, and hairless larva of a fly which North Americans call a maggot. A gusano is a thing "afuera" or outside, as the people say to distinguish it from a creature of similar appearance, a worm or lombriz, which is a thing from inside the earth.

The caterpillars of the brown tail and gypsy moths are found especially in New England. They provoke urticating dermatitis by direct contact or by shedding minutely barbed hairs which are blown about by the wind, finally coming to rest on the skin. Red macules and wheals form, which persist from a few days to several weeks. Itching is usually intense, especially if the hairs get into the clothing

The sharply pointed nettling hairs of these caterpillars are hollow and conceal a poison within the lumen which is injected into the blood stream when the skin is pricked. The entrance of the venom into the general circulation accounts for the cases of paralysis that occasionally develop in victims of caterpillar bites.

Rove beetles or picahuyes. These beetles are particularly active in northern Central America in spring and summer after heavy rains. Their body fluid contains a volatile substance *closely related to cantharidin but differing from it in that its* effect appears in one or two days after contact with the beetle. Beetles should not be swatted on the skin because this fluid coming in contact with the skin easily provokes bullous dermatitis. For the same reason it is best to drain off the fluid from these blisters

According to Lehmann, Pipkin and Ressmann, the various species of blister bugs found throughout the United States and Canada actually contain cantharidin and not a closely related oil. The cantharidin secreted by these beetles causes a vesicle or bulla to appear within a few hours.

Large bullae should be drained and then protected with an occlusive dressing. An antibiotic ointment may be applied.

Bedbugs or chinchas. These bugs are known to harbor the organisms of leprosy relapsing fever tularemia, Chagas disease, leishmaniasis bubonic plague and classic typhus fever However human infection from this source has not been proved.

Triatoma. This cone nosed bug is popularly known as vinchuca in Argentina and barbeiro in Brazil. It has a high vector potentiality for it transmits Chagas disease which is prevalent in Costa Rica.

Fleas or pulgas. Fleas are important intermediary hosts of the etiologic agents of bubonic plague and of endemic murine typhus fever of Mexico and the southeastern part of the United States. The grouping of urticarial wheals with a central hemorrhagic spot is typical of flea bites.

Fleas are regarded by Canizares and Shatin, Allington and Allington, and others as causing the majority of instances of acute papular urticaria. The proponents of the arthropod-bite etiology theory of this disorder believe that the individual hypersensitivity to arthropod antigens is especially widespread among children. However I recall the Viennese children with popular urticaria, in whom Urbach demonstrated hypersensitivity to various foods. The tests were carried out while the children were in the hospital, and the outcome of many hundreds of scratch and intradermal

tests led him to conclude that the disease is generally due to food sensitization.

Dermatophiliasis. This is an infestation with another kind of flea variously known as sand flea, chigoe, nigua, and Tunga penetrans, its occurrence chiefly in tropical countries leading to confusion with trombidiosis, a disorder caused by chiggers, not chigoes. Man is infected by contact with soil infested with immature fleas, the female burrowing into the skin and leaving the posterior part visible as a blackish spot, where papules and nodules soon make their appearance. These terminate as festering sores, and since the feet are the commonest location of the disorder it often leads to amputation of the toes. Involvement of the anogenital region of people who customarily sleep on the ground is by no means unusual, the accompanying pain being extremely severe.

The sores produced by niguas occasionally serve as ports of entry for the introduction into the body of pyogenic and other organisms. Out of a total of 31 instances of tetanus in Costa Rica, two were caused by entrance of the infection through sores on the feet, produced by niguas.

Pediculus capitis or piojo. This louse is destroyed by spraying a preparation composed of 10 parts DDT powder and 90 parts powdered talc on the patient's hair, a paper towel being placed over the eyes to prevent irritation. Shampooing and combing with a fine tooth comb are then carried out for seven days, when another application of the powder is made.

Vinegar does not soften the gelatinous coating that binds the nits to the hair. It has been demonstrated that this adhesive substance is not dissolved after soaking in a 10 per cent solution of acetic acid for several days. Rubbing one or two ounces of Cuprex, a proprietary solution of copper on the head is effective.

Pediculus corporis. This vector of rickettsias and Borrelia recurrentis might better be called the clothing louse because it deposits its eggs in the meshes of underclothing, only feeding on the skin. A thorough bath and autoclaving of the clothes destroys the lice.

Pediculus pubis or ladillo. The occurrence of bullous lesions in infestations with crab lice was reported by Kern. He believes

Botfly larvae also invade the nasal fossae and external ear where they sometimes cause extensive destruction of bone. Farmers have learned to suffocate them by inserting a plug of tobacco or sweet basil into the ear

A biopsy in insect bites generally shows intense edema and an extensive inflammatory reaction in the dermis over which the epidermis may or may not show pseudoepitheliomatous hyperplasia, sometimes confused with squamous cell carcinoma by general pathologists and others. The infiltrate in the dermis extends down into the subcutis and consists chiefly of eosinophils, lymphocytes, leukocytes, and a few plasma cells.

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The Cutaneous Helminthiases

By
Frederick R. Schmidt

Pathogenic worms live in animals, in bodies of water and in certain crustacea, whence fully developed larvae emerge as a source of irritation to swimmers. They are also found in food, drinking water and soil, from which they are transmitted directly or through the agency of arthropods to man and other mammals The Oribatid mites and certain insects serve as intermediary hosts for tapeworms and roundworms

The damage done to the skin by the invasion and emergence of the parasite is quite understandable. The occurrence, however of cutaneous lesions in patients with helminthic disease in areas far removed from the site of invasion and where there are no worms requires another explanation.

Experiments demonstrate that certain toxic substances liberated in the intestines of patients with helminthic infection cause reactions when absorbed. These toxins are probably freed after the dissolution of the parasite.

The existence of a toxic liquid in the celomic cavity of Ascaris lumbricoides serves as a specific example of toxic substances of this type. The occurrence of urticaria and prurigo in patients with helminthic infection may therefore be presumed due to these and other toxins associated with intestinal helminthic foci, because it is a noteworthy clinical observation that larval migrations in and about the gastrointestinal tract habitually provoke exacerbations of itching.

Schistosomiasis is caused by trematode worms, the final larval stages of which are known as cercariae. They cause swimmers itch or cercarial dermatitis, a disorder of frequent occurrence on the beaches and in the fresh water streams and lakes of Canada

and the United States. Cercarial infected marine snails capable of producing dermatitis in man are also being found in the waters around Cuba and Hawaii.

Cercariae live parasitically in snails from which they emerge and swim about freely in the water where they are viable for not more than 70 hours they can be seen in clear water with the unaided eye. Fish swallow the cercariae and are eaten by birds in whose droppings the worm is returned to the water

When man is infested by cercariae, an itchy papule soon forms at the site of penetration, and during the next week or so the victim is plagued with hives, itching, and tightness of the skin caused by subcutaneous edema. Visceral involvement does not occur because the cercariae die soon after penetrating the epidermis.

The principal methods of preventing schistosomiasis include the protection of water supplies from contamination with feces containing the ova of the parasite and the removal of snails by collection from the vicinity of bathing beaches. The latter procedure is not easy and Macy found that the application of copper sulfate and freshly hydrated lime in snow form off shore from the beaches was equally effective The chemicals are spread about by a power pump and settle down on the bottom of the lake where they are capable of killing snails for several years. Macy also recommends wiping the body vigorously with a towel immediately after swimming Persons engaged in occupations requiring wading in contaminated waters, as those spear ing fish in Puerto Rico and other islands of the West Indies, should wear rubber boots, for cercariae readily pass through ordinary clothing.

Urticarial swellings also occur in persons infected with types of worms other than trematodes, especially in Hawaii where infected fresh-water fish is eaten raw

Sinophores like the Portuguese man-of war and agua mala in the waters around Cuba have a toxic substance in their tentacles capable of producing burning and itching dermatitis in those happening to brush against them The velella, which resembles a tiny sailboat floating on the surface of the water and the dedalillo a form of coral life, also inflict sharp stings.

Tapeworms are carried from animals to man by arthropods, cutaneous cysticercosis being caused by Taenia solium which develops in both man and hog and finds its definitive host in man. Involvement of the skin is manifested as small, skin colored tumors called cysticerci that vary in size from 3 mm. to 2 cm. The histologic changes observed in material taken from an infected person show the cysticercus lined by a fibrous capsule and surrounded by a cellular infiltrate. There is no pain associated with these cystlike structures, and it is impossible to tell them from other swellings of similar appearance.

Ascariasis is very common in tropical countries. It is caused by Ascaris lumbricoides which is a large intestinal nematode that quite frequently provokes urticarial and papular eruptions in adults and children as clinical evidence of cutaneous sensitization to the toxins of the parasite inhabiting the gastrointestinal tract. Neither does Trichuris trichiura directly cause cutaneous lesions, but since it is coextensive in distribution with Ascaris lumbricoides and is found with Ascaris in contaminated water and food, it is highly probable that some of these eruptions are caused by sensitization to its toxins.

The pin worm, Enterobius vermicularis, is the causative agent of oxyuriasis, a disorder in which the female worm incites marked nocturnal pruritus as it wanders out of the anus and nips the skin in its quest for food. Pyoderma of the perianal region frequently occurs as mute evidence of scratching Kelly and Scott examined 200 Negro children in the Washington area and found seven positive for Ascaris and four for Enterobius. Their survey disclosed a lower incidence of pinworm infection in Negro children than in white children, a discrepancy which the authors believe is due to various factors. Among these are improved sanitation facilities in the area and the fact that their survey included many children who were hospitalized and therefore subjected to routine cleansing procedures, whereas children in other surveys were from summer camps and day nurseries.

Creeping eruption or larva migrans is caused by Ancylostoma braziliense and A. caninum, although the maggots of bot and warble flies as well as other larvae may produce a similar condition by burrowing under the skin The skin of the feet and

hands of children are most commonly penetrated, probably because children like to play in sand boxes and on beaches where the sand is damp Two types of dermatitis may result from this invasion. In one, the larva penetrates the skin and about four days later it starts to creep under the horny layer at the rate of a few millimeters a day building a raised and twisted line composed of papules and vesicles. Itching is intense and scratching often leads to infection. The other type is manifested as groups of papules and vesicles at the site of invasion, this form occurring particularly in A. caninum infestations and bearing a close resemblance to ground itch.

Allergic manifestations in the lungs and areas of the skin far removed from the site of infestation have been reported in several instances of creeping eruption.

The use of solid carbon dioxide, ethyl chloride spray or galvanocauterization is good treatment for this disorder The first two methods are effective if a small area of the skin is frozen ahead of the advancing end of the burrow The effective larvacidal action of various antibiotics and of hexylresorcinol in vitro and in intestinal infestations is not duplicated in cutaneous infestations, probably because the drug can not reach the skin in sufficient concentration to kill the parasite.

Uncinarial dermatitis is caused by one or more species of slender nematodes. Also known as strongyloids, the two species responsible for the disorder are Ancylostoma duodenale and Necator americanus. The larva generally penetrates the foot in barefooted persons, where it initiates a succession of erythema, vesicles, and blisters that frequently become complicated with cellulitis and lymphangitis. Intense itching sets in at once. This ground itch is usually the initial stage of generalized hookworm disease.

Trichinella spiralis is the cause of trichinosis, both larvae and adult worms reaching the skin by various routes. The earlier stage of the disease is occasionally marked by a bright maculopapular rash on the trunk and extremities. Later during the migration of the larvae, an edema of the face sets in, especially around the eyes, to give the patient a mongolian appearance. Urticarial wheals are sometimes observed.

Diagnostic features in trichinosis are a relatively low erythrocyte sedimentation rate, particularly in acute trichinosis, and a high eosinophil count.

The diagnosis is further facilitated by resorting to specific immunologic tests. A positive intradermal reaction made with 0.1 cc. of antigen derived from laboratory infested rats in a dilution of 1 7000 takes place immediately and reaches a maximum in about 10 minutes. Precipitin tests are diagnostic, using antigen dilutions of 1 100 to 1 1500

The possibility that trichinella is at least one of the precipitating factors in the production of periarteritis nodosa was suggested to Chana and me by the findings in a young Chilean woman. We made a diagnosis of polyarteritis nodosa on the appearance of the skin lesions which was later confirmed by biopsy findings. A precipitation test for trichinosis was positive in a dilution of 1 1280 a finding not infrequent in Chile where the incidence of trichinosis is high. A revaluation of the history showed that the patient had had an attack of illness highly suggestive of trichinosis just before she entered the hospital.

TREATMENT OF CERTAIN HELMINTHIASES

Schistosomiasis is most effectively treated with intravenous injections of tartar emetic, but other trivalent antimony compounds such as Fuadin and Repodral are preferred because they are less toxic. Both drugs are administered intramuscularly the dose for adults being 3.5 cc. of the 6.3 per cent solution (1 cc.–8.5 mg of trivalent antimony) the first day and 5.0 cc. the second and third days, 5 cc. are then injected every other day until 12 to15 injections have been given. Higher dosage is advocated by some authors. An accurate check should be kept on the urinary output.

It is by no means uncommon for patients to have a relapse after two or three months, in which case they should submit to another complete series of injections of either Fuadin or Repodral, especially if eggs are still being passed, or clinical symptoms persist.

Miracil D has recently been introduced as a useful remedy in schistosomiasis it has the advantage of being effective when given by mouth.

Ascariasis is effectively treated only when the infection is entirely intestinal, as it is not possible to destroy the larvae which have migrated beyond the intestinal mucosa.

The best therapeutic agent is papain, a crystalline proteolytic enzyme derived from the latex of the papaw Papain digests the keratogenous cuticle of Ascaris and thus allows the intestinal enzymes to penetrate and digest the worm. Since the eggs are not destroyed by papain, it is advisable to repeat the treatment in three or four weeks

I have used two products containing papain, Nematocid-Om and Velardon, they have the great advantage of being nontoxic.

An effective and less costly remedy is the oil of chenopodium, the dosage, however must be carefully controlled because of the drug s extreme toxicity It is contraindicated in pregnancy acute infectious diseases, severe circulatory disturbances, and disorders associated with damage to the hepatic cells. It is used as follows

Children	4 years of age	8 drops
	6	5
	8	6
	10	9
	12	10
	14	12
	16	15
	18	20

Adults should take 24 drops. Castor oil is given two hours after the drug, if thorough purgation is not obtained, the castor oil should be repeated.

The oil of chenopodium is often administered simultaneously with castor oil. In my experience, the use of hexylresorcinol in ascariasis has been disappointing

The recent report by Brown on the use of piperazine in the treatment of 51 Ascaris-infected children is encouraging These children were given a syrup containing piperazine hexahydrate by mouth for two to five consecutive days 46 children passed all of their worms as a result of a single course of treatment. This is a cure rate of 90 per cent.

There is no specific treatment for cysticercosis. Surgical excision is indicated for cysts which are causing pressure symptoms.

Tapeworms are best eliminated from the intestinal tract by the use of the oleoresin of aspidium (male fern) in doses not to exceed 8 0 gm. The patient is put to bed and given castor oil, on the following morning, a cup of black coffee with sugar is allowed one half hour before taking the oleoresin of aspidium The adult tapeworms are the easiest to destroy It is often necessary to pass a duodenal tube through which a little chloroform is injected, five minutes later castor oil and the oleoresin of aspidium are injected. This form of therapy is not recommended in patients with hepatic or renal disease It is contra indicated in pregnancy

A cure in oxyuriasis can not be obtained unless the patient cooperates in observing great cleanliness to prevent autoinfection. The objective of treatment is to eliminate the young worms from the small intestine and the sexually mature worms from the colon.

In order to prevent autoinfection which takes place especially at night, the patient is instructed to wear a pair of tight fitting swim trunks. This will prevent the fingers from becoming contaminated with eggs which the female worm deposits on the skin of the anal region as its leaves the anus in quest of food, inciting intense itching in this area. The swim trunks must be boiled daily The skin of this area should be lightly smeared with ointment of ammoniated mercury U.S.P to deter the worm s activity The hands and fingernails should be thoroughly scrubbed with hot water and soap before each meal.

According to reports in the literature the oral administration of a daily dose of oxytetracycline for seven days is 100 per cent curative in pin worm infection

During treatment, patients should abstain from eating carbohydrates and ruffage-producing foods, since pin worms thrive on these articles of diet.

Generalized h d best treated by tetrachlor ethylene given a mach. Thorough purgation is necessary this drug

There is no although ACTH has been re

In very early cases, the use of drastic purgatives and gastric lavage will sometimes hinder the worms from penetrating the intestinal wall. This procedure is useful, however only in cases in which the patient seeks medical advice immediately after having eaten contaminated meat. Once the trichinae have become fastened to the intestinal mucosa, medication is generally useless

A few drinks of hard liquor without much water are popularly believed to lighten the severity of the attack (vasodilator and antispasmodic)

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(*End of Dr Nevermann s contribution.*)

The filariform worms are nematodes of which the progeny are motile larvae named microfilariae. They must escape from the skin during the feeding of a blood sucking insect in order to complete their life cycle in the insect, after which they are carried to another host.

Filariasis loa is usually caused by Mansonella ozzardi transmitted to man by the mangrove fly a tabanid fly of the genus Chrysops, which also serves as intermediary host for the parasite. Characteristic of the disorder are the so-called calabar swellings of the subcutaneous tissues. Although the disease is not indigenous to the Americas, physicians should think of it in missionaries and other persons returning from long residences in endemic areas such as certain parts of Africa.

American onchocerciasis is caused by invasion of the skin and other parts of the body by Microfilaria or Onchocerca caucutiens which is transmitted to man by several species of the genus Simulium. These are popularly known as buffalo flies and abound in the forests of Mexico, Guatemala, and Venezuela.

The onchocercoma is a subcutaneous nodule resembling a cyst or lipoma and is the most common sign of the disease. It

is hard and not adherent to the underlying tissues, its chief location being the scalp, where it may perforate the cranial bones. In the beginning there is considerable edema of a livid green color around these cystlike formations, which later become hard and glossy as the disorder passes into the chronic stage in which the skin appears wrinkled and pigmented. Various hypersensitive manifestations such as lichenified and vesiculopapular dermatitis accompanied by intense itching may appear during the acute phase of the disease.

Since onchocercomas are frequently surrounded by a wide zone of sharply demarcated redness and swelling resembling classic erysipelas and because it affects the population of the Pacific coastal regions of Mexico and Guatemala, the term coastal erysipelas is used for what is regarded by many as a variant of the disease and by some as an acute complication. Although generally believed to be due to adult filariae or their toxins, recent studies have demonstrated the presence of streptococci in many of these patients. The eyes are affected in over 80 per cent of patients with onchocerciasis, and blindness results only too frequently

Dracunculiasis is a disease in which Guinea worm larvae migrate from the intestine to the skin and then outside. The infection was abundantly introduced by Negro slaves into the Guyanas Brazil, and the Caribbean area. Except for the possibility of isolated cases in areas remote from medical facilities, the disorder has probably died out in the Americas because the elimination of stagnant waters has destroyed the breeding places of Cyclops, the intermediary host of the Guinea worm.

Filarial elephantiasis, of which the etiologic agent is Wuchereria or Microfilaria bancrofti, is characterized by enormous swellings of the legs and genitalia. Chronic urticaria has been found associated with this microfilariasis. The disorder is fairly common along the northern coastal areas of South America and throughout the West Indies with a few endemic areas existing in Central America.

Elephantiasis is by no means always present in patients showing Wuchereria bancrofti in the blood, according to Lieske. This investigator also found that Culex fatigans is the dominant spe-

cies of mosquito in the Puerto Limon area and that this mosquito plays an important role in the transmission of filariasis.

Filarial elephantiasis must be distinguished from a similar swelling of the legs caused by the entrance of the streptococcus through openings in the skin resulting from fungous infections or other primary injuries. Repeated attacks of acute lymphangitis resulting from such infections induce thickening of the skin and swelling of the leg in a great many persons living in the tropics.

The positive diagnosis is made on finding the parasite in blood smears taken at night, although the parasite is often found in smears taken in the daytime. This is in contrast with Filariasis loa in which smears are only positive in blood taken in the daytime.

TREATMENT OF THE MICROFILARIASES

Hetrazan (diethylcarbamazine) has to a great extent replaced surgical extirpation of the onchocercomas, although in remote localities excision is still widely practised. Excision, however is not curative, because the patient is a reservoir of microfilariae which continue to infect him, spreading the infection to others through the agency of insects.

In onchocerciasis, Hetrazan should be given by mouth in doses of 2 to 3 mg per kilogram of body weight three times daily for two weeks, repeating the treatment six months later if necessary In other types of microfilariasis, a daily dosage of 3 mg. per kilogram for three or four weeks is usually adequate.

Suramin, a highly complex carbamide compound, is better than Hetrazan in infections with Onchocerca volvulus, the species responsible for African onchocerciasis Since most authorities regard Onchocerca volvulus and Onchocerca caucutiens as similar species, Suramin was tried in the Americas where it proved ineffective. Suramin is considered superior to Hetrazan because it causes death of the mature worms and slow disappearance of the microfilariae. Because of this, severe allergic reactions occur less often than after the use of Hetrazan, which causes rapid destruc tion of large numbers of microfilariae.

Persons with eosinophilia and intestinal symptoms of filarial infestation often do not respond satisfactorily to Hetrazan. They feel greatly improved and gain weight, nevertheless, microfilariae

persist in the blood smear In these persons, one should search for the existence of associated parasites. Ecker Lovshin, and Reich showed that this often occurs in South America in coexistent intestinal infestation with Acanthocheilonema perstans and Mansonella ozzardi.

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Odds and Ends of Dermatology

By
Frederick R. Schmidt

Acanthoma (Tumorlike Keratosis of Poth) The exact nosologic position of this condition is not clear It begins with reddish spots on exposed parts, particularly the face and hands, the lesions soon becoming raised and crusted, ultimately healing with light scarring. They are definitely worse in summer Reasoning from the absence of systemic symptoms and the light-sensitization distribution of the lesions, Weidman concludes that the condition is a light-sensitization dermatosis reaching its fullest development in the form of these tumorlike keratoses or acanthomas He also stresses the need for distinguishing it from lupus erythematosus.

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Acne vulgaris. The successful treatment of acne requires the use of remedies carefully chosen from a large number of therapeutic agents. If ever there is need for individualization in medical treatment, it is here. A judicious use of some or all of the following remedies is recommended

1. A few exposures to fractional doses of x rays are most helpful in lessening the secretion of the oil glands. This should be done at once and at frequent intervals in order to gain the confidence of the patient. As I look back upon my experience with acne patients who did not have at least a few x-ray treatments, I am convinced that to them I was just another doctor who gave them pills

and lotions and told them not to eat chocolate. Few of them re turned a second time

2. Enteric coated stilbesterol may be given in doses of 0.25 mg daily starting two weeks after the menstrual period. In male patients estrogen is also helpful in curbing the activity of the sebaceous gland. My experiences with progesterone have not been favorable. The use of anterior pituitrin extract in conjunc tion with drainage of the cysts is indicated in cystic acne.

3 Orally administered vitamin A in daily doses of 100 000 units is good adjuvant treatment for comedones

4. Anemia, so often associated with acne in young subjects, should be combated with large doses of ferrous sulfate. Likewise, patients with low basal metabolism should be given thyroid ex tract.

5 Existent foci of infection should be eliminated. Treatment with 2 gm. daily of sulfadiazine for two weeks often does wonders in the pustular types.

6. Control of coexistent seborrheic dermatitis of the scalp with Selsun or resorcinol monoacetate is essential.

7 Excessive exposure to sunlight or the ultraviolet lamp should be avoided, as it is common knowledge in the northern parts of the United States that the incidence of patients with fresh attacks or exacerbations of acne rises in August and September after the customary annual vacation.

8. The physician should constantly assure the patients of ulti mate cure. At the same time, he should at least attempt to straighten out the patient's mental conflicts and extricate him from any marital or social "traps."

9 Contact with grease, Diesel oil, and other petroleum products should be avoided. Workers with oily or hairy skin when ex posed to these substances frequently develop acne or folliculitis.

10 Daily intramuscular injections of 1 cc. of placental extract are often beneficial. It is my experience that if improvement fails to set in after 12 injections further treatment is useless.

11. Restriction of milk intake is probably the most important single dietary prescription.

12. Topical applications should be prescribed. It is advisable to wash the face twice daily with an acidulated sulfated oil deter

gent, avoiding vigorous rubbing with a washcloth or complexion brush. A sulfur preparation may then be applied.

13. Skin planing with the high speed rotary technique has come into vogue for the removal of acne scars This procedure may be carried out in the physician s office, the patient returning to the office daily to have the dressings changed. Heatless stone grinders have proved superior to steel wire brushes even though the brushes are furnished with perpendicular bristles. Refrigeration-anesthesia may be necessary

Acrodermatitis chronica atrophicans (ACA) An unusual feature of this disease is the occasional initial involvement of only one extremity with subsequent participation of other extremities. Cases beginning with unilateral involvement should be distinquished from a closely related dermatosis described by Pasini under the name of idiopathic atrophoderma, in which keloid formation sometimes takes place in the atrophic areas and at other times scleroderma supervenes. Intense itching is occasionally present in both ACA and idiopathic atrophoderma.

The cause of ACA is not clear It is difficult to assume an inherited weakness of the elastic fibers as the causative factor in view of the evidence showing that the elastic fibers in unaffected areas are not destroyed until the disease is well advanced.

Why is the elastic tissue destroyed only in areas invaded by the infiltrate? In my opinion the answer lies in the epidemiologic and histoanatomic features of the disorder

It has long been thought that most cases originate in the Vosges mountains of France and in the hilly regions of Czechoslovakia and Poland. Any doctor seeing how the inhabitants of the rural districts of these lands wash their clothes and trudge around barefooted in all kinds of inclement weather can not fail to think about the development of acute rheumatic fever and other "collagen diseases" resulting from exposure to cold and chilling. There is plenty of "rheumatism" among these people. If we accept the pathogenetic concept of arteriolar spasm induced by chilling in many cases of acute rheumatic fever it is logical to expect a similar precipitating factor in disorders exhibiting similar histoanatomic changes.

The pathologic changes in ACA present this similarity In histologic sections of early lesions, one sees dilated blood ves-

sels with endothelial proliferation and peripheral zones of inflammatory infiltration. In addition, the entire dermis shows scattered areas of lymphocytic infiltrates and interstitial edema. In more advanced lesions, there are also atrophy of the collagenous bundles and disintegration of the elastic fibers. Along with ultimate fibrosis, these are features commonly met with in most "collagen diseases."

The course of events in ACA thus parallels that observed in the "collagen diseases," and the symptoms of the disorder likewise find their explanation in the chain of pathologic tissue changes induced initially by arteriolar spasm and secondarily by degeneration of the collagen. According to this concept, the entire process is initiated by vascular reactions.

This theory of etiology and pathogenesis is strengthened by the occurrence of the disease in temperate zones of the Americas where many people go bare-footed and are often exposed to chilling, and by the rarity of the disease in warmer climates where the inhabitants also go bare-footed but do not suffer from the cold.

Acrokeratoelastoidosis. This new skin disease recently reported by Costa consists of horny verruciform, or lichenoid lesions of varying size and shape occurring mainly on the dorsa of the feet, the anterior surfaces of the legs, the dorsa of the fingers and wrists and the thenar eminences The lesions are yellowish and transparent. There are no subjective symptoms The histologic changes are suggestive of a nevoid anomaly with involvement of the collagen and elastic fibers

Examination of the photographs included in the article by Costa suggests a dermatosis of similar appearance, namely lichen corneus hypertrophicus. This much neglected condition also shows an ocreaform distribution of horny yellowish, hyperkeratotic elements which, in two patients whom I had under observation, were limited to the ankles and dorsa of the feet. The pathologic changes resembled those in Costa s patients, particularly if one concedes that fibrosis and sclerosis of the dermal connective tissue as occurred in my patients are natural consequences of the degeneration of collagen.

It is suggested that acrokeratoelastoidosis of Costa represents an individualistic response to scratching and therefore belongs in

the group of ocreaform disorders occurring as a secondary disease following scratching or nonspecific dermatitis. Further observation will probably determine its exact nosologic position

REFERENCE

Costa, O. G. Acrokeratoelastoidosis. *Arch. Dermat. & Syph.*, 70:228, 1954.

Allergy There are four dermatoses in which hypersensitivity is a proved causative factor namely acute cholinergic urticaria, erythematous toxic eruption, certain prurigolike dermatoses, and contact sensitization dermatitis. As to what constitutes the hypersensitivity factor there exists a sad lack of unanimity among allergists. The evidence in support of ingested food and inhalants as allergenic agents of cutaneous disease is inconclusive. My own experience with Urbach's Propeptones, dietotherapy and desensitization therapy was sadly disappointing Equally disappointing has been my experience with the antihistaminics. The swing at present, as far as the internal cause of hypersensitivity is concerned, is toward infection, particularly of the chronic type involving mainly the teeth and tonsils.

Duggan contends that the basic reaction of allergy is a reaction of the peripheral arterioles, regardless of the nature of the allergen thus the reaction may be of a physical or an antigen-antibody type.

Alopecia areata. Some 20 years ago, several French dermatologists found evidence of spasm occurring in the arterioles supplying the hair papillae of patients with alopecia areata. They also emphasized the frequency with which alopecia areata is associated with disorders in which the autonomic nervous system is involved, as exophthalmic goiter gastric ulcer and acrosclerosis. Petersen and I came to the same conclusion in the observation of patients with alopecia areata, in whom emotional stress was frequently the precipitating factor in provoking episodes of vasospasm. For this reason, Arnold's treatment with liberal doses of optimistic reassurance is still the best treatment for alopecia areata.

Annular constrictions of the extremities. In addition to annular bands occurring on the little toe and little finger in ainhum

(see p. 367) there are a number of other conditions associated with constrictions of this type. Rings of sclerotic tissue are occasionally found encircling one or more toes of newborn infants. This congenital anomaly differs from ainhum in that plastic surgery gives good results whereas in ainhum the end result is spontaneous amputation, surgery being of no avail. Injuries such as encircling lacerations as well as burns and frostbite sometimes heal with annular scars. Finally diseases such as leprosy, scleroderma, and syringomyelia should not be overlooked in this connection.

Calcifying epithelioma (Malherbe). In three unpublished cases of Jaramillo of Santiago, Chile which I observed and of which I still retain the histologic sections, the lesions consisted of hard, relatively deep-seated tumors, each about the size of a large marble. One of these little tumors was situated on the forehead and the other two on the arms above the elbow. All three patients were females; the average age of the lesions was 15 months. Ulceration did not occur in any of the lesions, as reported recently by Castigliano and Rominger; the absence of ulceration in Jaramillo's patients was probably due to the circumstance that the tumors in his patients were of relatively small size and recent appearance. If Jaramillo had not become aware of these little growths while studying with Darier and had not been such a keen diagnostician, the tumors would probably have been diagnosed as calcified cysts and allowed to grow in size until ulceration occurred. There was no evidence of malignant neoplasia in the histologic sections.

REFERENCE

Castigliano, S. G. and Rominger, C. J.: Benign calcifying epithelioma of the skin. *Arch. Dermat. & Syph.*, 70:590, 1954.

Chondrodermatitis nodularis chronica helicis. Patients with painful nodular growth of the ear often give a history of frostbite, *leading us to suspect* that the blood and oxygen supply of the affected area are sufficiently impaired by the frostbite to interfere with normal repair of both the soft tissue and cartilage. The interference with the blood supply is expressed clinically by a small

ulcer which is always found underneath the crusted or hyperkeratotic surface of the nodule. Because of poor vascularization, the use of x-ray radium, or carbon dioxide snow is contraindicated. The best results are obtained with plastic surgery

Congenital ichthyosiform erythroderma and ichthyosis. A 16-year old white boy entered the hospital in July 1954, complaining of inability to work because of the condition of his hands and feet. He stated that "he was born with a red skin" and that his brother had a similar condition.

The most striking presenting symptom was the thickened and fissured skin of the palms and soles. The feet gave off a fetid odor The original description of congenital ichthyosiform erythroderma by Brocq as quoted by Shelley and Crissey fitted the appearance of the palms and soles exactly "The hyperkeratotic process may affect the palms of the hands, and the soles of the feet to such a degree that it constitutes there an enormous mass of cornified material with a yellowish appearance, almost villous, nearly amber coloured, recalling the most developed arsenical hyperkeratosis"

Another feature emphasized by Brocq and observed in this patient was the condition of the nails, which were arched and tended to grow crooked. The patient stated that his hair and nails grew very fast.

It was decided to treat the patient with daily intramuscular injections of 100 micrograms of vitamin B_{12}. Foot baths of a weak solution of potassium permanganate were ordered to reduce the fetid odor Although the patient soon began to feel stronger there was no change in the cutaneous picture until after the twentieth injection, when an appreciable softening of the carapaced palms and soles occurred. By the thirty-fifth injection, the skin of the affected parts was considerably softer and the patient was able to flex and extend the hands with relative ease.

By March 15 1955, the patient had lost approximately two-thirds of the horny masses on the palms and soles. He feels well and is gainfully employed. Except for two periods of one week each, the injections have been given without interruption.

The patient's brother has not been able to have the injections of vitamin B_{12} and his condition has remained unchanged.

Applying this same form of therapy to patients with ichthyosis, treatment of this condition was started when it was noticed that the patient with congenital ichthyosiform erythroderma began to show improvement. The same dosage is being employed in these patients and considerable softening of the skin of the affected parts has occurred. Here, too the softening did not occur until after the twentieth to twenty fifth injection.

REFERENCE

Brocq, J L, in Shelley W B, and Crissey J T: *Classics in Clinical Dermatology* Springfield, Illinois, Charles C Thomas, 1953, p. 816.

Darier's disease (Keratosis Follicularis) The youngest patient with this disorder encountered in my practice was seven years old, and the oldest was 46. Both were males, the lesions appearing in the boy during the first year of life while the man first noticed the eruption when he was 30 years old There was no familial or hereditary factor in either case. Both patients showed characteristic clinical and histologic changes If we classify Darier's disease as a genodermatosis, its late occurrence in the man must be regarded as a hamartoma.

Large doses of vitamin A in the form of butter and capsules of fish oil were given to these patients. Although the man showed improvement only at first, the boy failed to respond at all, in fact, at the time of his last visit, he was considerably worse than ever Since then he was given a series of treatments with grenz-rays, with indifferent results, a treatment which he undertook against my advice to abstain from all kinds of radiation therapy including heliotherapy

Darier's disease should be distinguished from

1. Familial benign chronic pemphigus

2. Epidermodysplasia verruciformis. A 16 year old boy at present in the San Juan de Dios hospital, shows all the features of this disease, but one He has not as yet developed either basal-cell epithelioma or squamous-cell carcinoma. He has an extensive eruption of flat-topped, dirty yellow discrete and confluent hyperkeratotic lesions resembling verrucae planae, chiefly on the wrists, hands, forearms, cheeks, chest, ankles, and lower third of the legs.

There is keratoderma palmaris. He is mentally deficient, gives a confused history of attacks which might have been epileptic seizures. He "believes that he always had the eruption.

This case resembles others that I have seen in that: the lesions are dirty yellow in contrast with the brown or grayish color of the lesions in Darier s disease; the absence of mucosal lesions in con trast with their occasional occurrence in Darier s disease; the occasional presence of keratosis palmaris et plantaris, as in this patient, is also infrequently found in patients with Darier s disease or acrokeratosis verruciformis the absence of crusts and verrucous lesions; and finally as in Darier s disease, treatment is ineffective.

3. Acrokeratosis verruciformis (Hopf) Here again, the lesions are dirty yellow and not brown, and their localization mainly if not exclusively on the dorsa of the hands and feet serves to distinguish this disorder clinically from Darier s disease and epidermodysplasia verruciformis. The histologic examination is distinctive in that there is no vacuolization of the cells of the horny layer

Grinspan of Buenos Aires is a champion of the nevoid origin of epidermodysplasia verruciform and acrokeratosis verruciformis, basing his opinion on the failure to demonstrate a virus either by implantation on chicken yolk or rabbit cornea, the association with epilepsy or other nevoid malformations and the failure of x-ray therapy

Dermatitis herpetiformis. Patients with widespread dermatitis of this type, particularly when associated with intense itching, find quick relief in the bath tub. I saw several men with dermatitis herpetiformis, associated with severe itching who found immediate relief in the insulated prolonged flowing bath of a local hospital. This was constructed according to plans submitted by Riehl of Vienna and included a hammock and thermostat to per mit a person to remain in the bath for 24 hours a day at a constant temperature of 98 F A little cider vinegar is added to the water to insure acidity An ordinary large tub suits the purpose almost as well, as the patients discovered on returning home from the hospital. However persons with a dry skin do not do so well in the bath.

My results with large doses of nicotinic acid in fresh cases and exacerbations have been as favorable as those with the "specific drug, sulfapyridine. This is usually attributed to the inclusion of the pyridine radical in the molecule of both sulfapyridine and nicotinic acid, the latter being pyridine-3-carboxylic acid. My opinion, however is that the improvement is due solely to the vasodilating effect of nicotinic acid.

Fowler s solution is a good remedy for patients during the intervals between exacerbations.

Urbach and Wolfram s concept of a viral causation has been disregarded for some time. Many believe that there is a close clinical and pathologic connection with erythema annulare centrifugum, particularly in cases beginning with erythema annulare centrifugum and later showing the picture of dermatitis herpetiformis Others, like Borda, believe that an inborn familial disturbance of tetrapyrrhol metabolism is the cause. Progesterone deficiency has also been suggested.

Herpes gestationis. This disease is regarded by most but by no means all dermatologists as closely related to dermatitis herpetiformis. It may be that it represents a vascular reaction in response to a stress of pregnancy infection, or toxemia. It is also possible that some cases occur in Rh-negative mothers who have been sensitized by previous transfusion with Rh positive blood. Anti Rh antibodies may then develop which react to the Rh-positive red cells entering the maternal circulation The result is herpes gestationis.

REFERENCE

URBACH, E., and WOLFRAM, S. The virus of pemphigus and dermatitis herpetiformis (English translation by F R. Schmidt.) *Arch. Dermat. & Syph.*, 33 733, 1936.

Endometrial tissue in the skin. Endometrial tissue is occasionally found at the umbilicus and in laparotomy scars At the umbilicus, it occurs in the form of small, bluish nodules which increase in size, pain, and tenderness at the menstrual periods. There is external menstrual bleeding in some cases In laparotomy scars, as occurred in one of Quiroga s cases, endometrium is

present in the form of small or large, tender nodules usually lying deep in the abdominal wall. The nodules generally invade the muscle and fascia, thus becoming fixed. In contrast with the bluish hue of the umbilical nodules, the lesions implanted in laparatomy scars are brown.

There are two theories of histogenesis one, that endometrial tissue is implanted in the abdominal wall at the time of operation, and the other that remnants of the original celom capable of endometrial differentiation are normally found at the umbilicus.

Erythema elevatum diutinum. This disorder does not enjoy a secure position in dermatology Although currently regarded by most authorities as an entity characterized by symmetrical, red to purple nodules occurring in men between 40 and 60 years of age, there are some who frankly admit that they can not recognize it. The disorder has been variously regarded as a closely related form of erythema multiforme granuloma annulare, or granuloma faciale. It is resistant to treatment, including x ray therapy

Erythema elevatum diutinum should not be confused with a disorder bearing an almost similar name in Spanish, eritema papuloso elevado y persistente. This disorder acquired its name in Argentina and is closely related to lupus erythematosus and actinic dermatitis. The subject is discussed by Corrales in his chapter on skin diseases caused by sunlight.

Erythema multiforme. There is a feature associated with fresh lesions of erythema multiforme which has not received much attention in the literature. It consists of a pearly white halo surrounding the lesion it is ephemeral, lasting only a few hours. The white color of the halo is an expression of increased arteriolar tone (vasospasm) for this reason, vasodilators are highly indicated in the early phase of this disorder

Another little-recognized feature of erythema multiforme is its occasional occurrence as the first evidence of leprosy In a Cherokee Indian woman observed in Chicago, there were successive crops of what Ormsby used to call erythema multiforme-urticaria symptom complex. Fresh lesions consisting mainly of papules and wheals appeared throughout a period of two months. The true nature of the underlying disease was finally detected when the patient's daughter told us that she was afraid of living with

her mother because the doctors had told her that her mother had leprosy Subsequent examinations showed this to be the case.

Erythema perstans. Regarded as either a variant of erythema multiforme or as frank dermatitis herpetiformis, erythema perstans has been recorded under a variety of names. As erythema annulare centrifugum, the disorder in many instances bears close resemblance to dermatitis herpetiformis in its clinical and pathologic features. Some cases may be dermatophytids, as reported by Jillson. The variety described by Wende as erythema figuratum perstans is probably synonymous with erythema annulare centrifugum, both varieties beginning with flat papules and forming lesions with hard, elevated margins, whose hardness is due to intense edema rather than cellular infiltration. The remaining varieties consist of single or multiple circinate and gyrate lesions which persist for a few days only

A similar appearing lesion to the single ring variety of erythema perstans, known as erythema chronicum migrans, was observed in Central America following tick bites. This lesion also lasted only a few days.

REFERENCE

JILLSON, O. F Allergic confirmation that some cases of erythema annulare centrifugum are dermatophytids. *Arch. Dermat. & Syph.*, 70:355 1954.

Favre-Chaix disease. This is the Spanish and Latin American equivalent of vasculitis or capillaritis It appears spontaneously without previous or associated ulceration and without evidence of varicose veins Pigmented and purpuric lesions, somewhat resembling those in progressive pigmentary dermatosis, are usually present. The central portion of the affected area is usually sclerotic i.e. Millian's white atrophy

Granular-cell myoblastoma. When Tuta and I first called the attention of North American dermatologists to granular-cell myoblastomas of the skin in 1942, the nature of the large acidophilic granules contained within the cytoplasm of the tumor cells was unknown. According to Lever several investigators believe that granular-cell myoblastomas are composed of either schwannian cells or endoneural fibroblasts. Other investig[illegible] ave told me

that the granules react positively to the periodic acid-Schiff technique, in which case the granules are probably composed of mucopolysaccharides.

REFERENCES

LEVER, W. F.: *Histopathology of the Skin*, Ed. 2. Philadelphia, London, Montreal, Lippincott, 1954, p. 441.
TORN, J. A., and SCHMIDT, F. R. So-called myoblastoma. *Arch. Dermat. & Syph.*, 46:225, 1942.

Hidrocystoma. An uncommon disorder of the face and neck in which usually a number of small, isolated, subepidermal cysts appear on otherwise normal skin. Occasionally however as happened in a patient observed in Chile, a solitary lesion may occur developing to the size of a marble. This patient was a 42-year old woman whose occupation as cook exposed her unduly to excessive heat. As a result of this exposure, a marble-sized, tense, deep-seated cyst developed in the skin immediately below the right eye.

On histologic examination, the excised cyst consisted of a large cavity lined by two layers of epithelial cells. The histogenesis of these cysts is not clear many believing that they are caused by simple retention of sweat in the sweat ducts with consequent dilatation of the ducts, while others think that they are caused by active proliferation of the sweat duct epithelium.

Hyperhidrosis. The use of Banthine bromide in oral doses of 50 or 100 mg. tablets three or four times daily prevents the action of acetylcholine on the effector organs of cholinergic nerves. In this way the cholinergic "sympathetic" nerves to the sweat gland are blocked. The drug also blocks the ganglions of the autonomic system. Pro-Banthine bromide is effective in smaller doses.

Idiopathic atrophoderma of Pasini. This rare form of macular atrophy of the skin is characterized by spots or patches of a violaceous color which are surrounded by an erythematous halo. The center of the lesion is depressed below the level of the surrounding skin. One's first thought is of scleroderma until the palpating finger finds a soft, normal skin. The histologic changes are those of the "collagen diseases." South American authors empha

size the importance of distinguishing this type of macular atrophy from Oppenheim's dermatitis atrophicans maculosa and Jadassohn's anetoderma erythematosum.

Keratosis pilaris. This disorder is well treated by nightly scrubbing with 5 per cent salicylic acid soap Keratosis pilaris belongs in the group of diseases having spinous elements, including lichen spinulosus and phrynoderma.

Miliaria. Sweating should be reduced to a minimum by a restriction of activity and by wearing as little clothing as possible. Patients should be instructed to mop up sweat as soon as possible, change their clothes often, take frequent shower baths, and wear loose fitting underdrawers to avoid chafing No more fluid should be taken than is necessary to quench the thirst. The ingestion of adequate fresh foods and sodium chloride is recommended. The following preparation is effective.

℞	Menthol	1.0
	Zinc oxide	16.0
	Alcohol (50%) sufficient to make	120.0

Patients should be instructed to apply anhydrous lanolin to involved areas two or three times daily as necessary The purpose of this is to dissolve the keratin rings surrounding the orifices of the sweat ducts.

The observations of Sargent and Slutsky seem, in my opinion, to warrant the use of the adrenocortical hormones in severe cases which do not respond to routine management.

Infants with this disorder should wear light clothing and be dusted frequently with a dusting powder In more severe cases, calamine lotion N.F may be utilized

Miliaria or lichen tropicalis. Lichen tropicalis is synonymous with miliaria in many parts of Spanish America.

Panniculitis, febrile atrophying. This appropriate term was suggested by Pardo-Castello to designate the condition known to English speaking dermatologists under the unwieldly name of relapsing febrile nodular nonsuppurating panniculitis. The condition was originally described by Gilchrist and Ketron and although generally regarded as one of the more or less infrequent disorders of the skin, it is in point of fact by no means uncommon

Its supposed uncommonness is due to diagnostic difficulties encountered in the early stages of the disease.

Three patients were observed in very early phases of the disorder. Two were young women, while the third was a 44 year old woman. All three complained of constitutional symptoms of malaise, muscular pains, and diarrhea. Fever was present. The youngest woman had several deeply situated, tender hard infiltrations varying in size from 3 to 5 cm. located on the upper arms and thighs. The lesions and symptoms in the other two women were similar. The attack lasted about a week in each patient, leaving several saucerlike, depressed scars. In none of the women did the infiltrations break down to discharge an oily or fatty yellowish-brown fluid, as occurred in two other cases.

It is difficult to distinguish this condition from similar hard, deeply situated infiltrates occurring in scleredema adultorum, scleroderma, sarcoidosis, and erythema induratum. In my experience, the differentiation from scleredema offers the greatest difficulty because of the similarity of the infiltrates. Those of sarcoidosis and erythema induratum are of smaller size.

From an etiologic and pathogenic standpoint, febrile atrophying panniculitis and scleredema adultorum resemble each other in that they are both manifestations of peripheral vascular disease induced by infection. The two younger women in my series had no further attacks after tonsillectomy was performed, and the older woman remained well after several badly infected molars were extracted.

Peculiar pigmentary disorder of unknown origin. A 12 year old white girl developed numerous discrete, pea-sized, brown macules on the neck, trunk, upper arms, and thighs a few days after exposure to the tropical sun while swimming. The lesions appeared suddenly in the affected areas, some of which had been covered by the swimming suit. There was no itching. On stroking the skin, many of the lesions became reddened and elevated, a phenomenon which did not occur at the time of later examinations. The lesions showed no tendency to coalesce. The eruption has persisted for two years, although it is tending to fade in many parts. There has been no treatment other than topical applications.

Histologic sections were examined by Dr Fred Weidman, who reported that he was unable to find evidence of urticaria pigmentosa (mast cells)

The absence of mast cells in an otherwise typical case of urticaria pigmentosa finds a possible explanation in the work of Drennan and Beare cited by Lever on page 58 of the second edition of his excellent book on histopathology Drennan and Beare according to Lever demonstrated that biopsy sections performed shortly after the lesion had been stroked occasionally show disintegration and a temporary disappearance of mast cells.

Pellagrous dermatitis following use of antibiotics. A 44 year old white woman entered the hospital with an erythematobullous eruption limited to the exposed parts of the body In addition, the legs showed a few bullous elements. The appearance of the face resembled that of acute disseminated lupus erythematosus. The patient was acutely ill with febrile manifestations and diarrhea.

She gave a history of having had influenza, for which she had been given penicillin injections. She also took aureomycin at the same time. The rash appeared following the seventh injection of penicillin. She denied the taking of alcoholic drinks.

Examination for L.E. cells in the blood and hematoxylin-staining bodies in the tissue was negative The biopsy examination failed to disclose evidence of lupus erythematosus.

Quinacrine was administered orally on the assumption that we were dealing with a case of polymorphous light eruption. This was discontinued when the patient grew noticeably worse Becoming discouraged, she left the hospital.

About this time, I came across the article by Morris, in which he reports three cases of true pellagrous dermatitis following the administration of antibiotics. His patients were quickly c d by the oral administration of nicotinic acid and by cold compresses Since prompt recurrence of the dermatitis place in his patients when they stopped taking nicotinic Morris concludes that the interference in nicotinic acid me lism caused by antibiotic medication is probabl iar

An analogous situation, in my opinion is r ine deficiency of seborrheic dermatitis.

REFERENCE

Moses, G. E.: Pellagrous dermatitis following use of antibiotics. *General Practitioner* 9 71, 1954.

Phrynoderma. This is only one manifestation of vitamin A deficiency It is important to remember that the fully developed picture of phrynoderma is by no means common. Furthermore, it is misleading to say that the distinguishing feature of the eruption is hyperkeratosis, for patients in the early stages of this condition usually show only dryness, roughness, and wrinkling of the skin. If treatment is started early in the course of the disorder hyperkeratinization of the conjunctival and corneal epithelium does not occur

This condition is by no means rare in Spanish America, although advanced cases with extensive hyperkeratoses and facial involvement were not encountered.

Porokeratosis Mibelli. This is a genodermatosis in which the method of inheritance is one of regular dominance. There is a possible relationship between this condition and vitamin A. The presence of mucosal lesions is mute witness to its erroneous designation as porokeratosis and indicates that the characteristic lesion, the cornoid lamella, is not necessarily located in the opening of a sweat duct. A patient observed in Quiroga s clinic had a roughly oval, sharply demarcated, flat, milky colored lesion on the right buccal mucosa. The slightly raised margin was better felt than seen.

The best results that I have seen in this disorder were obtained with the use of the spoon curette to destroy the cornoid lamella and with the galvanocautery for treatment of the central portion of the lesion.

Prurigo. This name should be applied exclusively to the disorder which begins between the first and fifth years of life as intensely itching papules localized on the arms and legs. Depending on its further course, prurigo is malignant or benign. The symptomatology is identical in both types, but the ferocious character of the itching and the widespread distribution of malignant prurigo seriously affect the general health of the patient, in contrast with the mildness of symptoms in benign prurigo. Pa-

tients with prurigo generally feel more comfortable in the summer

Hebra originally divided prurigo into prurigo ferox and mitis, which I have just called malignant and benign prurigo, respectively I believe that the tendency to regard prurigo ferox and prurigo nodularis as synonymous with circumscribed neurodermatitis is unjustified.

The cause of prurigo is not clear Various hypotheses advanced to clarify the situation have not been substantiated. It is probable that a number of causative agents are capable of precipitating episodes of itching and crops of lesions, as in urticaria. Among these factors are hypersensitivity toxic products of digestion, disturbed metabolism of unknown nature, and emotional stress.

When a descriptive adjective is added to prurigo, it is no longer true prurigo. Prurigo nodularis is an uncommon disorder appearing at any time of life. It is characterized by reddish-brown, firm, rounded nodules usually located on the arms, legs, and back, and occasionally on other parts of the body These nodules are intensely pruritic. The histopathology is distinctive. There is a considerable bulk of evidence supporting an allergenic factor However treatment directed against the hypersensitivity factor is usually fruitless

Prurigo and prurigo nodularis are thus clearly defined clinical and histopathologic entities. Prurigo does not develop from papular urticaria, as Ormsby concluded from the observation of a great number of children with papular urticaria whom he observed in London with Colcott Fox. Urticarial complications not infrequently occur in early phases of prurigo, but they are not prurigo.

It is suggested that the terms, Besnier's prurigo and Brocq's acute prurigo of children and adults which are widely used in Spanish America, be stricken from the literature as confusing and irrelevant. For all other dermatoses associated with typical papules of prurigo, with or without lichenification, it would be better to use the term, prurigolike Thus

1 Actinic dermatitis associated with prurigolike lesions appearing particularly in the V-area of the neck and chest.

2. Atypical prurigolike papules confined to the lower extremities appearing in crops each winter to disappear in summer

3. Large dome-shaped nodules resembling those of prurigo nodularis, appearing chiefly on the arms. These large prurigo-like lesions are associated with erythema and in advanced cases with lichenification as well. They occur mainly in persons living at high altitudes, such as the western parts of the United States, around Guadalajara in Mexico and the central plateau of Central America. The eruption is recurrent. In two patients observed in Costa Rica, uroporphyrin was not found in the urine.

Pseudo-acanthosis nigricans. Curth pointed out in numerous publications on the subject that this disorder occurs only in obese, darkly pigmented individuals. She also states that the cutaneous changes between the breasts similar to those described by Gougerot and Carteaud as papillomatose confluente et reticulee may be a feature of pseudo acanthosis nigricans."

In a patient with Gougerot and Carteaud's disease observed in Quiroga's clinic, the lesions consisted of small, greyish, verrucous, papillomatous papules which had appeared in crops on the chest and neck and in the axillary interscapular and sacral regions. The individual lesion was difficult to distinguish from nevus verrucosus In Quiroga's opinion, the only distinctive feature of this disorder is the reticulated character of the lesions at the border of the affected areas, whereas Curth sets it aside from acanthosis nigricans by pointing out that the course of true acanthosis nigricans is independent of obesity and its accompanying mechanical features.

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Curth, H. O In material exhibited in Scientific Exhibits. Annual Meeting of the American Academy of Dermatology Palmer House, Chicago, December, 1949.

Psoriasis. The effective treatment of psoriasis with vitamin B_{12} by Bonilla-Dib deserves especial consideration, so excellent have been the results. I have been privileged to observe more than 20 patients treated in this manner and Dr Bonilla has kindly permitted me to give a short summary of his results.

Most of the patients in this series had received routine treatment for psoriasis, often including the Goeckermann technique,

all types of local applications, intravenous salicylic acid, autohemotherapy Fowler's solution, ACTH or cortisone. Eighty per cent of these individuals had had the disease for many years. All were highly skeptical of receiving benefit from the injections.

The treatment consists of daily intramuscular injections of 1000 micrograms of vitamin B_{12} given without interruption until involution of all lesions takes place. Five per cent ointment of ammoniated mercury U.S.P is prescribed for all patients

In a few patients 35 to 40 injections were necessary before there was noticeable improvement. Most patients, however showed definite flattening of lesions by the tenth injection in three patients only ten injections were required to clear the eruption.

In spite of the high dosage used in this form of therapy it was not necessary to prescribe iron in a single case. Almost every patient spoke of feeling stronger Seven patients suffered a relapse when they stopped treatment too soon but upon its resumption, improvement soon took place with complete involution of lesions

When patients with seborrheic dermatitis were subjected to this therapy the results were contradictory The first patients of this series were given daily intramuscular injections of 1000 micrograms of vitamin B_{12} until it was noticed that the lesions of practically all patients grew worse soon after the fifth or sixth treatment and that the patients complained of not feeling well. When, however the dosage was reduced to 100 micrograms daily improvement soon became manifest in about 50 per cent of these individuals. It was finally concluded that patients with seborrheic dermatitis are sometimes benefitted by vitamin B_{12}, although the results are unpredictable.

Rat-bite fevers. The rash when present, differs in the two forms of this disorder *In the spirillar type of infection known as sodoku* the site of the bite heals without showing much inflammatory reaction, until one day the patient becoming acutely ill with severe muscular pains chills, vomiting, and prostration, it rapidly becomes painfully swollen and acquires a purplish color Lymphangitis of the draining lymphatic vessels occurs, the severity of the inflammatory reaction with the subsequent lymphatic

involvement ranging from mild changes to necrosis. The flare-up at the site of the bite is associated with a generalized macular eruption that begins on the abdomen with bluish red, slightly elevated macules having sharply defined borders. This roseola slowly pales as the patient feels better Then suddenly after a short respite of several days, the patient suffers a relapse which is of even greater severity than the first attack. He notices that his spots have come back larger and darker than before. These erythematous, indurated patches of the later stages are relatively few in number and asymmetrically disposed.

In the streptobacillary form known as Haverhill fever the site of the bite is not inflamed nor does lymphangitis occur The rash consists at first of reddish maculopapular elements that are met with in great numbers in symmetrical areas on the hands, arms, and feet in contradistinction to the asymmetrical pattern of the large, erythematous, indurated patches in sodoku. Petechial elements with swelling around the joints soon appear arthritis being the most persistent symptom of the disorder

The diagnosis is made on the appearance of the rash, by the demonstration of the causative agent in the blood, and by the outcome of the specific agglutination reaction Spirillum minus colors readily with Giemsa s stain. The agglutination test is generally made with dilutions of 1 15 and 1 100 Both Spirillum minus and Streptobacillus moniliformis are found in the blood and urine of infected persons, sometimes one or the other organism being isolated and at other times although rarely both.

Syphilitic chancre, cellulitis, erysipelas, and furuncle should be considered in the differential diagnosis Although of rare occurrence in the United States the spirillar form is met with in Mexico and certain countries of South America, and it is in these countries that confusion occasionally arises with murine typhus fever and other intermittent fevers.

The therapeutic agent of choice in sodoku is aureomycin and in Haverhill fever penicillin.

Rh factor in skin diseases. A 23 year old nongravid woman with acute disseminated lupus erythematosus was given a blood transfusion as a measure of last resort. She was in a critical condition, having failed to respond to any of the recognized

therapeutic agents available in the pre-steroid days. She responded indifferently to the transfusion, and it was decided not to give a second one.

Ten days after the transfusion, she suddenly became severely ill, and a second transfusion was performed four days later. One hour later she was in shock. Oxygen was administered. She remained anuric and in a deep stupor for four days, after which she slowly recovered. The cutaneous lesions and laboratory symptoms of the disorder disappeared, and the patient is well today eight years after her illness.

The donor's blood showed no blood-group incompatibility. However, after the second transfusion it was discovered that the donor was Rh-positive and the patient, Rh-negative. Her grandparents on her mother's side were Basques, so that she is what is called a 2-name Basque. Statistics show that 20 per cent of 2-name Basques are Rh-negative, this woman being a member of this group.

A plausible explanation of what happened in this case is that the woman became critically ill following the second transfusion because she had been sensitized by the Rh-positive red cells of the donor's blood. The interval of 14 days between the two transfusions had enabled her to build up sufficient anti-Rh antibodies to cause a severe reaction to the Rh-positive red cells of the donor's blood immediately following the second transfusion.

Although isosensitization by the Rh factor apparently cured this patient of acute lupus erythematosus, the risk incurred with this form of shock treatment has deterred my colleagues, to whom I have recounted the history of this case, from using such a dramatic therapeutic agent.

It will be recalled that the Rh factor is not the only antigen occurring in the red blood cells of man. The antigens of the ABO system are also inherited factors which persist unchanged throughout life. Of a similar nature, although not inherited, are the specific anticellular antibodies such as the antimesenchymal opsonins. The possibility of these antigens being the cause of lupus erythematosus was recently discussed by Capelli.

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CAPELLI, E. Theoretical basis and experimental production "in vitro" of the L.E. phenomenon in blood of normal persons by means of human antireticulo-endothelial serum: Is lupus erythematosus a disease of antibodies? cited by Sulzberger, M. B., and Baer, R. L. *Year Book of Dermatology and Syphilology* Chicago, Y. B. Pub., 1953–1954, p. 201.

Sarcoidosis. The tuberculous origin of sarcoidosis is still staunchly championed in spite of the fact that the majority of sarcoid patients show a negative reaction to the injection of tuberculin. The failure of these patients to respond to tuberculin is looked upon as an indication that the tuberculous process is in an anergic phase due to the specific relative anergy of the host. It is maintained by many that this specific relative anergy to tuberculin occurring in most sarcoid patients must be distinguished from the nonspecific anergy to tuberculin displayed by patients with measles and other disorders.

The studies carried on by Rostenberg and his associates and by Sones and Israel comprise a large part of the evidence tending to cast doubt on the validity of the existence of specific relative anergy to tuberculin in patients with sarcoidosis. Rostenberg and his associates inoculated a number of sarcoid patients as well as a number of patients with diseases other than sarcoidosis with living BCG organisms and living M. smegmatis or B. subtilis and found no evidence to support either the theory of specific relative anergy to tuberculin or that of a tuberculous origin for sarcoidosis.

The observation that sarcoid patients occasionally develop frank pulmonary tuberculosis with disappearance of the cutaneous lesions and conversion of tuberculin negativity to positivity does not support the theory of tuberculous origin. Even though this development could result from the irritation provided by the causative agent of sarcoidosis or its products of disintegration, as occurs in pulmonary silicosis, other observations of a similar nature tend to mitigate against the tuberculous origin of sarcoidosis.

One of these observations is the occasional development of sarcoid lesions toward lepromatous leprosy. In a patient observed in Bolivia, this occurred four years after the establishment

of a clinical and histoanatomic diagnosis of sarcoidosis If one argues that this patient had the indeterminate or borderline type of leprosy which then developed toward lepromatous leprosy never having had sarcoidosis at any time, it is equally correct to maintain that patients with histologically proved sarcoidosis, who later develop pulmonary tuberculosis, originally had tuberculosis and not sarcoidosis.

The failure of patients with cutaneous sarcoidosis to develop frank tuberculosis or leprosy following the use of BCG vaccine also speaks strongly against a tuberculous or leprous causation. Not only do these individuals fail to develop frank manifestations of these diseases but the histologic changes in the inoculation papule or in lesions existing at the time of the inoculation are not those uniformly found in tuberculosis or sarcoidosis

The response of patients with proved tuberculosis or leprosy to the Kveim antigen is a feature worthy of consideration. It has been demonstrated that the majority of such patients have a negative reaction to the Kveim antigen making it doubtful whether or not the antigen contains *M tuberculosis, M. leprae*, or their derivatives.

The subject is further complicated by the denial of the very existence of cutaneous sarcoidosis as an independent disease by many authorities in Mexico. They maintain that all sarcoid-like lesions of the skin are manifestations of leprosy They base their conviction on the similarity of clinical and not infrequent histoanatomic alterations of the skin, bones, and other organs as well as on the immunologic response to lepromin and the reversal of this reaction from negative to positive through the use of BCG

It would nevertheless be injudicious to reason from these observations that sarcoidosis is not in some way connected with tuberculosis or leprosy The conclusions drawn from many years of clinical experience do not warrant such a deduction.

The histoanatomic findings in cutaneous sarcoidosis are suggestive of epithelioid and giant cell reticulosis. By way of comparison, two other disorders with somewhat similar findings merit attention.

One of these is benign inoculation lymphoreticulosis (cat scratch disease) in which the histologic appearance of the infected lymph nodes is that of a reticular reaction. This resemblance to early sarcoid disease of the skin is enhanced by the presence of inclusion bodies which have been found by Schaumann as well as Lever and Freiman.

Another disorder having somewhat similar features is lymphogranuloma venereum. It is likewise characterized by widespread distribution throughout the body diversity of clinical manifestations, the presence of inclusion bodies, and the tendency to fibrosis displayed by the disease process in its involuntary phase.

The nature of the inclusion bodies occurring in patients with sarcoidosis is uncertain. These bodies, however in the lymph nodes of patients with lymphogranuloma venereum and benign inoculation lymphoreticulosis have been proved identical with the elementary bodies of the viruses responsible for these disorders.

Such observations suggest that sarcoidosis is caused by a virus The presence of inclusion bodies, however within giant cells in the healing phase of cutaneous sarcoidosis is by no means conclusive evidence of a viral causation It will be recalled that the ability of many viruses to induce inclusions in their host cells is neither common to all viruses nor is it possessed exclusively by viruses. Furthermore, the presence of inclusion bodies does not indicate sarcoidosis or virus disease, because they are also present in the cutaneous granulomas of berylliosis

Other disorders with which sarcoidosis is occasionally associated are histoplasmosis and periarteritis nodosa. Histoplasmosis is a disease involving the reticuloendothelial system and periarteritis nodosa is regarded by many as a vascular manifestation of hypersensitivity

In view of the foregoing, I would like to suggest that sarcoidosis is a reticular reaction to hypersensitivity which may be induced by an as yet unidentified virus or a variety of other infectious agents.

The treatment of this disorder is unsatisfactory the response of patients to drugs being erratic. I have found the use of terramycin attended with better than average results.

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Scleredema adultorum. A 23 year old white woman complained that her skin, particularly of the neck, shoulders and upper parts of the chest and back, was hard and "lumpy" This condition had persisted for 10 years following an attack of influenza. The patient, upon her return to her home in Hawaii, was examined by Dr Harry Arnold, Jr., who made a diagnosis of scleredema adultorum.

A white woman, 42 years of age, entered the hospital complaining of pain in her arms and shoulders. On examination, the skin and subcutaneous tissue of these parts as well as of the neck was found to be indurated. She had had an attack of grippe two years earlier and ever since had noticed stiffness of the neck and shoulders. Her teeth were in poor condition. The extraction of all infected teeth in conjunction with intravenous procaine therapy resulted in considerable improvement.

These two cases emphasize the occasional chronicity of scleredema adultorum and the part played by an antecedent infection in its production. The possible development of generalized scleroderma in these patients should be considered.

Seborrheic dermatitis. This disorder is an entity occupying a position halfway between chronic eczematous dermatitis and psoriasis. It is possibly associated with local cutaneous pyridoxine deficiency (see p. 420) The histologic distinction from psoriasis and circumscribed neurodermatitis is often difficult. However Caro states that seborrheic dermatitis shows greater edema, a denser infiltrate, and more parakeratosis than psoriasis. In circumscribed neurodermatitis on the other hand, the epi

dermis shows longer acuminate rete pegs than in seborrheic dermatitis and there is less parakeratosis.

In extensive eruptions of seborrheic dermatitis, involving the entire head, neck, and chest, a trial with daily injections of 100 micrograms of vitamin B_{12} is recommended.

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CARO, M. R.: Diagnostic Pitfalls of Dermal Pathology. *Arch. Dermat. & Syph.*, 67:18, 1953.

Sturge-Weber Syndrome. The recent report of King and Schwarz concerning a hitherto unreported complication of this syndrome is of interest to dermatologists. In one of the patients studied by these authors, there was a calcified subdural hematoma ipsilateral to the facial nevus flammeus and intracerebral calcification.

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KING, G., and SCHWARZ, G. A. Sturge-Weber syndrome (encephalotrigeminal angiomatosis). *Arch. Int. Med.*, 94:743, 1954.

Telangiectasis macularis eruptiva perstans. I am afraid that I *cannot distinguish this from the eruption frequently seen in* adult patients with urticaria pigmentosa. Both conditions are characterized clinically by persistent, red macules with scarcely any pigmentation and histologically by an infiltrate consisting mainly of mast cells.

Mast cells secrete heparin, hyaluronic acid, and histamine. These "heparinocytes" are widely distributed in the connective tissue of the body. In the normal skin, they are present in relatively small numbers, occurring mainly along the smaller blood vessels and around the hair follicles.

Recent studies of patients with urticaria pigmentosa led Konrad and Winkler to conclude that the rapid formation of interstitial fluid evoked by stroking the lesions is due to the increased capillary permeability induced by heparin secreted by the mast cells. In commenting on these conclusions, Sulzberger and Baer point out that Konrad and Winkler fail to produce evidence of the presence of a specific hypersensitivity factor in urticaria

pigmentosa which could account for the formation of wheals when the skin is stroked.

There is one objection to this comment. A statement of this kind implies that the lesions of urticaria pigmentosa *always* urticate when the skin is stroked. I remember cases, however in which the stroking of certain lesions caused them to urticate, while others did not urticate. Furthermore, upon subsequent examination of these patients, the lesions which had urticated previously did not urticate again. Thus, a definite pattern can not be set for urtication in this disorder

The explanation of this phenomenon may lie in the presence of histamine in the mast cells, rather than in the presence or absence of a hypersensitivity factor Thus it is also possible that the interstitial edema comprising the wheal is the result of increased capillary permeability induced not by heparin but by histamine released from the mast cell. The vasodilating effect of histamine, however may not always be operative, in which case urtication does not take place. For some reason or other the supply of histamine becomes temporarily depleted.

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Thrombocytopenic purpura. A nine year old white girl was recently admitted to the San Juan de Dios hospital complaining of weakness, loss of appetite, and frequent chills Her temperature on admission was 101.2 F Scattered in irregular fashion over the body were a number of dark, fuzzy-edged patches, whose color did not fade on pressure. The patches varied in size from 5 to 15 cm. The mother stated that the spots had first appeared some 10 months previously Examination of the blood revealed no abnormalities other than a blood platelet count of 36 000 per cubic millimeter Subsequent platelet counts were around this level, although never dropping below 35 000. The parents refused permission for a splenectomy

About that time I ran across an article by Belber Davis, and Epstein, in which these authors report a case of thrombocytopenic purpura occurring in a patient with cat-scratch disease and cite this as an example of purpura caused by a virus. It seemed ages until my patient returned for observation and I could ask her whether she had a cat. She finally did return, and she had a cat which was always scratching her

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BELBER, J P DAVIS, A. E., and EPSTEIN, E. H. Thrombocytopenic purpura associated with cat-scratch disease. *Arch. Int. Med.*, 94:321, 1954.

Ulcer tropical. This disorder which might better be called tropical phagedenic ulcer is found most commonly in tropical countries with an average yearly temperature of 70 F Ulcers of this kind have raised, slightly undermined margins and occur most frequently on the legs and occasionally on any part of the body The infection is derived from soil and grasses, barefooted persons being most often affected during the rainy season.

Treatment of this disorder has been greatly facilitated by the advent of the antibiotic drugs. Ziprkowski, Rein, and Kitchen recently reported cures in 14 patients with a single intramuscular injection of 1,200 000 units of penicillin procaine in oil and aluminum monostearate (PAM) This therapy does away with the hitherto prevalent necessity of complete bed rest in a hospital. Patients with tropical ulcer are usually undernourished.

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By

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